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CONTENTS

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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

Vol. XLVII. JULY, 1953 No. 3.

EDITORIAL

THIS issue calls for a brief editorial note since, with the publication for the first time of a Special Supplement, a precedent is created in the history of the Journal.

The Supplement, presented to all regular subscribers to the Journal, is published through the generosity of the South African Council for Scientific and Industrial Research, who have made a special grant towards its publication on the recommendation of our South African representative on the Editorial Board, Dr. B. A. Dormer.

In our Festival Number in 1951 we anticipated broadening the scope of the Journal by inviting colleagues from the Dominions to serve on the Editorial Board. Since their joining us in January 1952 this hope has been achieved, and valuable regular contributions from the Dominions have culminated in this Special Supplement. The work, sponsored by Dr. Dormer, and carried out in his department by Dr. D. J. M. Jenkin, is a preliminary report on a new method of intracavitary injection in the treatment of pulmonary tuberculosis.

It is frankly admitted that the treatment is, up to the present, of an experimental nature, but we feel that any contribution it can make towards cavity closure and sputum conversion deserves consideration. The method claims to be of value in certain selected cases of chronic cavitating pulmonary tuberculosis, hitherto regarded as infectious, incurable and unsuitable for major surgery. The indications and contra-indications are carefully outlined.

Dr. Dormer, Dr. Jenkin and their associates hope that wider use of this method may result in improved technique, and we trust that this Special Supplement may lead other workers to use the method and thereby a critical assessment of its value may ensue.

PROBLEMS OF TUBERCULOSIS IN INDUSTRY

A STUDY OF THE SHOEMAKING TRADE IN NORTHAMPTONSHIRE

By Alice Stewart

From the Social Medicine Unit, the University of Oxford

"The root idea with which I began the work was that every fact I needed was known to someone and that the information had simply to be collected and put together."—*Charles Booth, "Life and Labour of the People in London," 1892.*

The belief that shoemakers are particularly prone to tuberculosis is not new, and when the newly formed Medical Research Committee—precursor of the Medical Research Council—decided to study the incidence of phthisis in relation to occupation they turned first to the shoemaking industry. A special investigation committee was appointed and in 1915 a report, based on national statistics of mortality, was published (M.R.C. Committee, 1915). The report stated that there was definitely more tuberculosis in the trade than elsewhere and that, in the opinion of the authors, this was due partly to predisposition to the disease and partly to an excessive amount of infection. The recommendations included improved ventilation of workshops and regular periods of rest and exercise during factory hours, but greatest stress was placed on "a modified form of sanatorium treatment." The latter was, in effect, a scheme to segregate the tuberculous shoemakers and provide them with suitable work and regular medical supervision for the rest of their working lives. The plan was worked out in considerable detail, but when, in 1947, the medical profession was reminded that there was still an excessive amount of tuberculosis in the boot and shoe industry, it also learnt that none of the 1915 recommendations had been adopted.

On this occasion it was a Mass Radiography survey of factory workers in Northamptonshire which focused attention on the trouble by revealing "an excess of newly discovered cases of active pulmonary tuberculosis" among workers in boot and shoe factories (C. M. Smith, 1947). Exaggerated accounts of the dangers of making shoes appeared in the daily press and both sides of the industry agreed that a comprehensive medical investigation should be made. A steering committee under the chairmanship of Dr. C. M. Smith (Medical Officer of Health for the County) was formed and in July 1947 an investigation was launched which had, from the outset, the active assistance of manufacturers and operatives.

At this time the established facts all derived either from national statistics of mortality (Registrar-General, 1881-1931) or from the official report of the Northamptonshire Mass Radiography Survey. According to the former, the death rate for pulmonary tuberculosis among male shoemakers had been exceptionally high at least since 1891. The original Medical Research Committee report was based on the Census returns for 1891, 1901 and 1911 and made

(*Received for publication December 17, 1952.*)

it clear that the high tuberculosis death rate was unusual inasmuch as it was not accompanied by a high rate for other causes of death. Later returns (1921 and 1931) also showed that the death rate for pulmonary but not other forms of tuberculosis was higher among "boot and shoe factory operatives" than among "makers and repairers" (non-factory) (see Fig. 1). The report on the Mass Radiography Survey, in addition to demonstrating that there were more cases of active tuberculosis in boot and shoe factories than elsewhere, also showed that the excess was common to both sexes and to two age groups

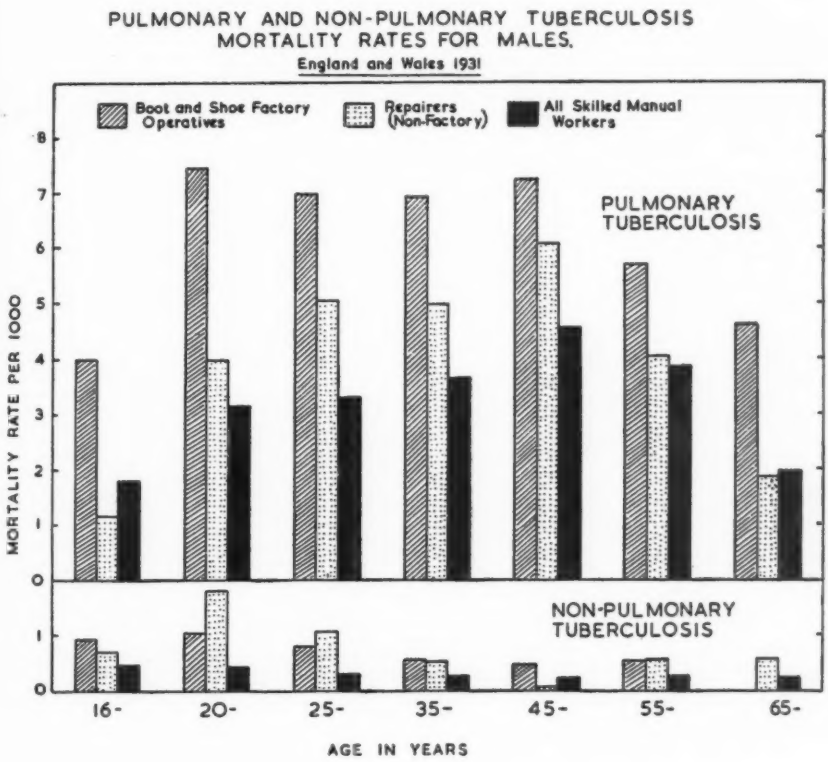

FIG. 1.

(under and over 35 years), but was greatest among the men in the older age group.

Informed opinion in Northamptonshire extended much further than established fact and manufacturers, operatives, factory inspectors and doctors all subscribed to the view that the problem was a legacy from the old outwork system and that, but for the war and the relatively late development of the factory system (*circa* 1900-1914), it would already have disappeared. It was also thought that leather dust was at the root of the trouble, and authorities on the subject were unanimous in forecasting that the older and less well-

equipped factories—which incidentally tended to be much smaller than the modern factories—would be found to be harbouring most of the cases.

When, however, mortality trends were studied in relation to wages and working conditions it was found that although there had been, during the period of records (1881-1931), an absolute and relative improvement in the social and economic status of the shoemakers as well as an absolute improvement in the tuberculosis death rate, nevertheless the trend of tuberculosis mortality among shoemakers *relative* to that of all other manual workers—

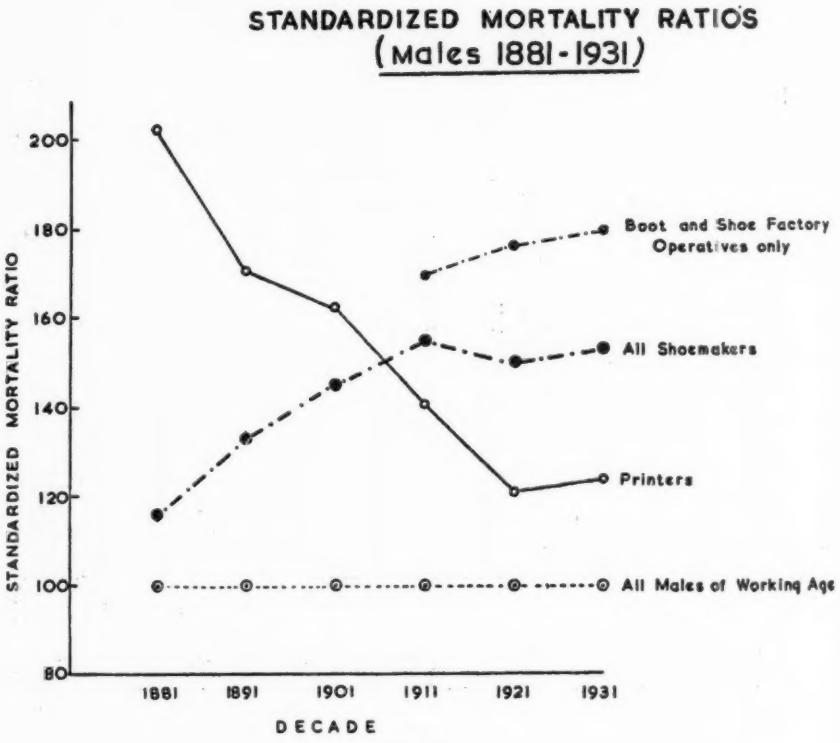

FIG. 2.

and printers in particular—was distinctly unfavourable (see Fig. 2). Even more unexpected was the discovery that, judging by the Mass Radiography findings, the larger the factory the greater the prevalence of the disease (see Fig. 3).

The complete absence of any evidence of pneumoconiosis in the Mass Radiography films also suggested that, whatever the role of leather dust in the etiology of shoemakers' phthisis, it did not, like coal or quartz dust, lower resistance to tuberculosis by producing pulmonary fibrosis. At this stage in the investigation it was decided to reject the lung damage theory. In its place was erected the working hypothesis that "shoemakers' phthisis" was not,

strictly speaking, an industrial disease, but merely an unusually clear example of the sequence of events which can be and frequently is associated with our present *laisser-faire* policy towards the employment of tuberculous persons in industry.

According to this theory (i) the relative excess of tuberculosis in the boot and shoe industry as a whole is due to the presence of an exceptionally large number of tuberculosis carriers in the working population; (ii) the unequal distribution of cases within the industry is due to the fact that in large work-

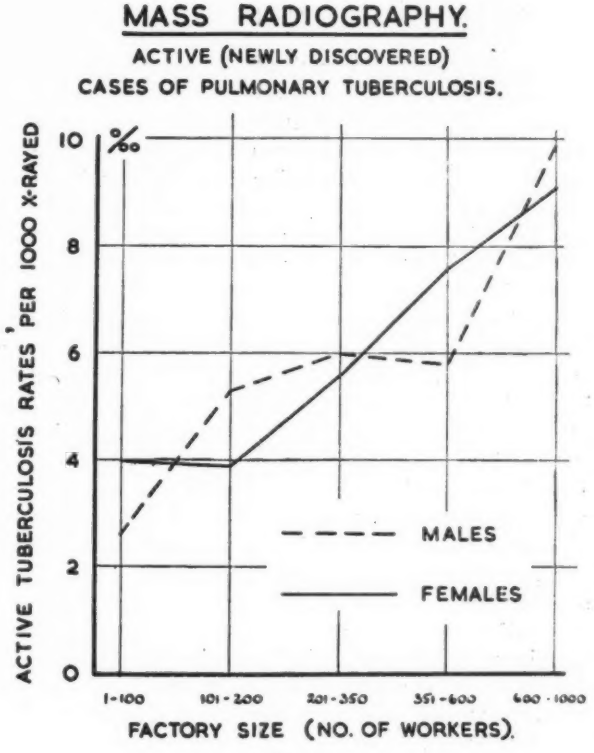

FIG. 3.

shops the spread of infection from carriers to fellow-workers is greater than in small ones. It was argued that since shoemaking is, for men, a relatively light occupation the industry probably recruits more established cases of tuberculosis than most industries. For the same reason it probably permits men who develop the disease on the job to remain at work much longer than if the work were excessively strenuous. In this way the carrier rate is still further augmented. Provided the men with chronic phthisis work on their own, as do most shoe repairers, their presence causes no further harm to the industry as such. But if, as in the case of boot and shoe factory operatives, they work in large groups the disease spreads to others. The extent of this

spread is influenced by the usual factors such as age, sex and previous exposure to the disease, but, other things being equal, it is likely to be greater in large groups of workers than in small groups. Finally, to account for the opposite trends of mortality for shoemakers and printers, it was postulated that the migration of operatives from cottage workshops to factories, which is a feature of every industrial revolution, is liable to provoke a relatively slow rise in the tuberculosis death rate followed by a subsequent fall (*i.e.*, a slow-motion epidemic). Provided, therefore, there is in any trade a nucleus of carriers, the date of its industrial revolution determines whether its tuberculosis death rate, relative to the national rate, is rising, falling or remaining stationary.

Needless to say such a far-reaching theory demanded more facts than could be extracted from the records of a single Mass Radiography survey and the Registrar-General's analysis of the deaths relating to six national Censuses. But although a few first-hand observations were made before the investigation was completed, it was mainly by exploring existing records that the working hypothesis was eventually established on a firm statistical basis.

The relationship between factory size and prevalence of tuberculosis, originally observed in the Mass Radiography records, was later explored in terms of official notifications, and nearly 500 boot and shoe operatives notified in Northamptonshire during the decade 1940-49 and belonging to the labour force of some 250 factories eventually contributed to the evidence. For each one of these factories the annual working population by sex, age, occupation and room distribution had as far as possible to be reconstructed, and for each notified case the occupation and last place of work had to be identified. When all these facts had been assembled, and the bacterial content of the air in nearly 200 workshops examined, it was possible to show that, with existing ventilation arrangements, both the prevalence of tuberculosis and the concentration of non-pathogenic bacteria in the atmosphere are profoundly influenced by the number of workers per room, but barely, if at all, affected by the actual spacing of workers within the room.

It was not possible to carry out tuberculin tests on a large scale, but the possibility that the acquired and/or innate resistance to tuberculosis of shoemakers was unduly low was explored, on the one hand by examining the original films of the Mass Radiography Survey to observe the distribution of healed tuberculosis foci, and on the other by interviewing representative samples of workers in different occupations and ascertaining parental occupations and family histories of tuberculosis. The first of these two inquiries, by revealing more healed or quiescent tuberculosis among boot and shoe operatives than among other workers, suggested, though it did not prove, that the acquired resistance of shoemakers was above average. The second, by showing that in given occupations there was slightly less tuberculosis among the sons and daughters of shoemakers than among the sons and daughters of other men, also pointed to a relatively high level of resistance to tuberculosis and effectively ruled out the "predisposition" theory.

Finally, the suggestion that shoemaking suits the limited capabilities of men with chronic tuberculosis was tested partly on the basis of the original Mass Radiography Survey and partly by examining the medical records of

men called up for National Service. Both sources showed that the number of notified cases of tuberculosis among shoemakers was exceptionally high and the call-up records also demonstrated that both the physique and the medical grade of the shoemakers were slightly substandard.

It is beyond the scope of this paper to describe either the steps that had to be taken to "standardise" the findings for different groups or the exact mathematical relationships which were finally established. These are described elsewhere (see Bibliography) and can be summed up in two ways. In

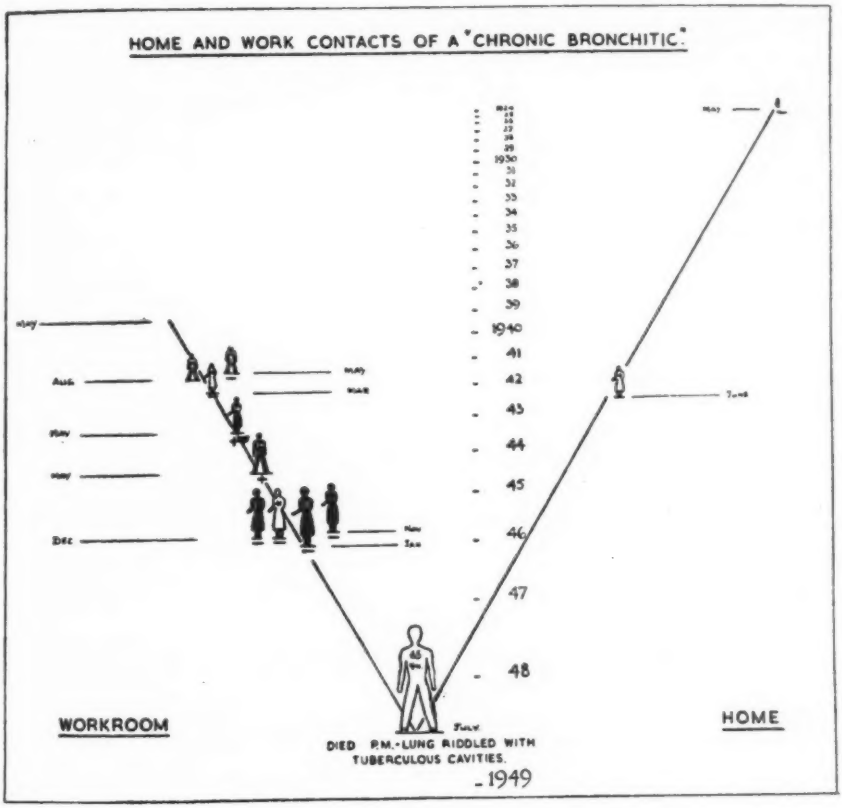

FIG. 4.

the first place the statistics suggest that for every ten boot and shoe operatives who contracted the disease from a relative there were eighteen to twenty who probably contracted it from a fellow-worker. Secondly, for a shoemaker working in a room with about 200 other operatives the risk of contracting tuberculosis was over three times as great as for a shoemaker working on his own.

Those who prefer something more tangible than statistical estimates should also glance at Fig. 4, which represents the actual findings in one of the

workshops included in the investigation. In this room of nearly 100 workers four cases of tuberculosis were discovered by the Mass Radiography Survey. All the cases were among women, only one of whom had any known contact with the disease. For all four cases the sputum examinations were negative. Later on it was discovered that five other persons, whose last place of work was in this room, had been notified between 1940 and 1945. All nine cases were, however, relatively acute and there was nothing to suggest a common source of infection until December 1948, when a death of a man aged 58 was reported to the authorities. Both the wife and daughter of this man had died of tuberculosis but he had somehow escaped examination. The factory records showed that he first began to work in the room specified above in September 1939 and that he remained there till he left the factory in August 1948. He attended work fairly regularly but refused to be examined when the Mass Radiography Unit visited the factory in 1946. He died within four months of leaving the factory and post-mortem examination revealed widespread tuberculous disease with cavities in both lungs.

This sequence of events reminds us that Mass Radiography surveys are bound now and then to fail in detecting dangerous sources of infection, but there is no escaping the general conclusion that if the combing-out of cases by Mass Radiography could be combined with a scheme for segregating them from other workers it would go far towards eliminating disease in the boot and shoe industry. When, however, we tried to advocate action along these lines we found on the one hand a manufacturers' association and a trades union whose attitude was "Why should we tackle what is clearly a national problem?" and on the other, a profession which firmly believed that the present system of allowing tuberculous subjects to return to industry was safe.

One thing seems clear: unless further evidence is forthcoming to convince the medical profession that spread of tuberculosis in factories is a greater menace to the community than spread in the home, the second boot and shoe investigation is likely to prove as fruitless as the first. Since it is unlikely that the opportunity to make a similar investigation in another industry will occur in the near future it may be worth while to put on record the findings of a small "domiciliary" survey which, in an effort to trace all contacts, combined Mass Radiography and tuberculin testing. The investigation was prompted by the fact that in a village of just under 1,000 inhabitants seven cases of tuberculosis had been reported to the authorities within four years. To discover what lay behind this exceptionally heavy incidence it was decided to X-ray as many adult members of the population as could be assembled, to tuberculin test and X-ray all the school children, and to identify the age and sex distribution (as well as the milk supply) of every household. Intensive propaganda produced all but one of the school children and nearly 85 per cent. of the adults, all of whom were questioned about tuberculosis contacts. Only one new case of active tuberculosis was added to the list of seven, but fourteen cases of healed or inactive tuberculosis and forty-four positive reactors among the school children were discovered. All the cases of tuberculosis except two in the inactive group, and all but five of the positive reactors among the school children, came from households which were completely represented in the survey. Further analysis showed that two of the

positive reactors came from a known tuberculous household and three from households in which an inactive case was reported. A further thirteen had a tuberculous relative living elsewhere and seven came from households which obtained their milk direct from a farm. But for the remaining nineteen children who were tuberculin positive there was nothing to indicate the path of infection.

An alternative way of expressing these results would be to say that a follow-up of home contacts of known cases of tuberculosis in the village would have led to the identification of 4·5 per cent. of the positive reactors. Additional follow-up of all inactive cases revealed by mass radiography would have brought the total up to 11·4 per cent., and complete family check-up of index cases living elsewhere (nephews, nieces, cousins and grandchildren being included in the term "family") would have identified a further 29·5 per cent. Yet when all these steps had been taken there would still have been nearly 60 per cent. of infected children left in the village. Taken alone this small investigation has nothing to contribute to the problem of tuberculosis in industry and merely hints that the tracing of home contacts is even less illuminating than we are accustomed to think. Combined with the boot and shoe investigation, however, it suggests a reason why we have taken so long to appreciate that nowadays the "flow" of infection is not from the homes to the factories but from the factories to the homes. For, such being the case, all that the tracing of home contacts can do is either to lead us farther away from the main source of trouble or to take us back a very short distance. It is in fact as though we were given a fairly clear picture of the capillary system but, never having seen the heart or main vessels, were not in a position to know in which direction the blood was flowing.

If the "pressure head" of infection really lies in the factories, then our present policy of encouraging tuberculous subjects to return to industry as soon as they are fit is wrong and should be replaced by one in which tuberculous persons, while given every other consideration, are forbidden to mix with other factory workers. It will of course be argued that the man who knows that he has tuberculosis is a much less dangerous source of infection than the man who unknowingly has the disease. But although the careful training and scrupulous behaviour of many individual patients justifies this opinion, there is some evidence that known tuberculous subjects are, as a group, a very real source of danger. There were, for instance, among the boot and shoe operatives who attended the 1945-46 Mass Radiography Survey thirty-five men who had been in sanatoria and were still nominally under medical supervision and 10,100 men who had no previous history of tuberculosis. In the first group the proportion of open cases of tuberculosis (*i.e.*, tubercle bacilli found in the sputum at the time of the survey) was just over one in eight and in the second group just under one in 400. But even if treated cases of tuberculosis were never infectious it would still be extremely difficult for social legislators to distinguish between them and untreated cases, for to do so would merely invite confusion. In fact the only social remedy that could be relied upon to free the factories from infection would be "a modified form of sanatorium treatment" for all tuberculous workers.

In conclusion, none of the researches described in the present paper sup-

ports the view that shoemaking should be scheduled as a "dangerous" occupation. The fact that the trade today has a high tuberculosis rate is partly due to an historical accident—that the change over from domestic to factory production occurred in comparatively recent years—and partly to the attraction which all light work has for persons susceptible to, or clearly suffering from, tuberculosis. But the tuberculosis risk of shoemakers is, in principle, a risk of infection, and as such is common to all factory employment.

BIBLIOGRAPHY

MEDICAL RESEARCH COUNCIL (1915): *First Report of the Special Investigation Committee* upon the Incidence of Phthisis in Relation to Occupations. London: H.M.S.O.

REGISTRAR-GENERAL (1881-1931): Decennial Supplements for England and Wales: Occupational Mortality. London: H.M.S.O.

SMITH, C. M. (1947): *Med. Offr.*, **77**, 109.

PUBLICATIONS RELATING TO PRESENT INVESTIGATION

CAIRNS, M., and STEWART, A. M. (1951): *Brit. J. Soc. Med.*, **5**, 73.

HEWITT, D., and STEWART, A. M. (1951): *Brit. J. Soc. Med.*, **5**, 209.

STEWART, A. M. (1952): *Proc. Roy. Soc. Med.*, **45**, 14.

STEWART, A. M., and HUGHES, J. P. W. (1949): *Brit. Med. J.*, **i**, 926.

STEWART, A. M., and HUGHES, J. P. W. (1951): *Brit. Med. J.*, **i**, 899.

THE SIGNIFICANCE OF UPPER LOBE ATELECTASIS DURING ARTIFICIAL PNEUMOTHORAX*

By Geoffrey L. Brinkman

From Cashmere Sanatorium, New Zealand

Since the introduction of effective chemotherapy for the treatment of pulmonary tuberculosis, the use of artificial pneumothorax has declined considerably. Not only is this because good results may be obtained without resorting to collapse therapy, but because artificial pneumothorax has been recognised as the precursor of many serious complications. In those parts of the world where inadequate surgical facilities exist, this form of collapse still has to be used more frequently than it would otherwise. In association with chemotherapy it may, however, prove to be a much more effective and less threatening form of treatment than artificial pneumothorax alone. Although artificial pneumothorax is nowadays restricted to carefully selected cases, complications still occur. For this reason the significance of upper lobe atelectasis occurring during the course of artificial pneumothorax must be recognised for what it is—a harbinger of trouble—and not regarded as a good example of "selective collapse" or as a "therapeutic thoracoplasty."

In the last three years several accounts have been published on the significance of atelectasis in artificial pneumothorax. Maher-Loughnam reviewed 2,750 cases of artificial pneumothorax, and amongst these he found 58 cases which had had a mechanically perfect pneumothorax but had subsequently relapsed. All 58 cases had had an area of atelectasia—often of only segmental distribution—preceding their relapse. Houghton investigated 50 consecutive empyemas complicating artificial pneumothorax, and of these 50 cases he found 43, or 86 per cent., had had an antecedent atelectasis of the underlying lung. Mitchell also found a higher incidence of empyema in cases in which there had been an atelectasis beforehand. On the other hand, Mary Farquharson investigated 100 cases of atelectasis in artificial pneumothorax and concluded that it was not a serious complication. Such findings are conflicting and it is hoped to clarify the position.

Observations

This investigation is based on 358 cases of artificial pneumothorax induced at Cashmere Sanatorium, New Zealand, from 1939 to 1948 inclusive. Only those artificial pneumothoraces that were maintained for at least three months have been reviewed. Chemotherapy was not in use at this time, so that its use does not complicate the results.

Of the 358 cases there were 49 with atelectasis of the upper lobes which persisted for over three months. Of these 49 cases, 19 progressed to a massive

* This paper is based on part of a thesis submitted for the degree of M.D. in the University of New Zealand.

(*Received for publication January* 29, 1953.)

atelectasis of the whole lung and have been excluded from most of the subsequent analyses. Of the remainder there were 13 examples of right upper lobe atelectasis and 17 of left upper lobe atelectasis. This is in contrast to the findings of Mary Farquharson, who states that because of the anatomy of the bronchial tree, atelectasis of the right upper lobe is three times as common as atelectasis of the left upper lobe. No case of segmental atelectasis was included, as lateral films were not available in most cases and interpretation is difficult on a posterior-anterior film alone.

In all 30 cases the atelectasis occurred within three months of induction and most were re-expanded within a year, although some persisted for two years. No example of atelectasis of under three months' duration has been included in this series, as it was apparent that no complications occurred in such cases. There was no connection between age and sex and the incidence of atelectasis.

Predisposing Factors

An atelectasis cannot always be predicted, but as a result of this survey two predisposing factors emerged:

1. 40 per cent. of these patients were toxic (as judged by the temperature, pulse or sedimentation rate) at the time of induction.

2. The best indication as to whether an atelectasis will occur is obtained from the pre-induction X-ray. Mitchell has demonstrated that "heavy" lung shadows in the pre-induction film predispose to a poor prognosis. This finding has been corroborated here, in so far that 90 per cent. of cases had "heavy" shadows in the pre-induction film. The X-ray appearances are so typical that in most cases it is possible to make a correct prediction of atelectasis.

Coello and Nagley (1948) have already described four types of X-ray appearances predisposing to atelectasis:

1. A fan-shaped area radiating out from the hilum.
2. Multiple cavities.
3. A ground-glass appearance.
4. Reduced hemithorax due to mediastinal shift, crowded ribs, or an elevated diaphragm.

Of the 49 cases in the Cashmere series only 35 are classified under the types listed by Coello and Nagley. Of the remaining 14 cases, 13 clearly belonged to a fifth group. This group consists of those cases with a solitary cavity in the upper lobe, the cavity being of the "tension" type.

It can be seen therefore that 48 out of every 49 cases can be grouped into one of these five types.

Complications

The high incidence of complications in artificial pneumothorax is the main reason for criticism of this form of collapse therapy. The commonest complications are spread of disease or fluid formation, and this last may lead to empyema with its attendant evils.

Fluid.—This is of common occurrence during artificial pneumothorax, and minimal amounts may come and go without any serious ill effects. For that reason, only when fluid was sufficient to cover the dome of the diaphragm was it recorded as significant.

In a control series of 220 cases of artificial pneumothorax induced during the same period, but in whom no atelectasis occurred, fluid developed in 16 per cent. In the atelectatic series 50 per cent. developed fluid.

Spread of Disease.—This occurred while the artificial pneumothorax was being maintained, in 37 per cent of the atelectatic series, as compared with 30 per cent. in the control series. This is not a significant difference.

The combination of spread of disease and fluid occurred in 12 per cent. of the atelectatic series and in 14 per cent. of the control series.

Type of Atelectasis

Coello has divided atelectasis of the upper lobe into two types, one said to be potentially dangerous and the other not.

Type I.—The lobe is shrunken and triangular in shape. Complications are said to occur infrequently and the prognosis is good.

Type II.—The lobe is tense and rounded. Complications are more frequent and the prognosis is poor.

One of the main difficulties encountered in trying to classify cases into these two types is that the X-ray appearance of the atelectatic lobe varies from time to time. In the Cashmere series there were 19 cases which could definitely be so classified.

Table I.—The Classification of 19 Cases of Upper Lobe Atelectasis according to the Scheme of Coello, showing the Number of Relapses and Deaths

	Type I	*Type II*
No. of cases	11	8
Relapses	7—64 per cent.	5—63 per cent.
Deaths	5—46 „ „	3—38 „ „

It can be seen from Table I that in this small series there was no appreciable difference in the two types. There must be some doubt, then, as to the validity of dividing atelectasis of the upper lobe into these two types.

Results

The final judgment of any form of treatment in pulmonary tuberculosis must rest on the long-term results. It is, therefore, necessary to compare the mortality rate for those cases in which atelectasis occurred with a comparable series in which atelectasis did not occur.

Two control series have been obtained. The first is based on an investigation (Butterfield, 1949) of 219 sputum-positive cases diagnosed during the years 1939-43. These were unselected consecutive cases. Of these cases 13 per cent. were dead at the end of one year from the time of diagnosis and 46 per cent. were dead at the end of six years.

The second control series is more selective and is confined to 100 consecutive cases treated by artificial pneumothorax during the years 1939-44 in whom no atelectasis of lobar or greater proportions occurred. The mor-

tality in these cases was 10 per cent. at the end of one year, and by the end of six years had risen to 25 per cent. with 7 per cent of cases still active.

The atelectasis series also covers the period from 1939 to 1948, and in these cases only 3 per cent. were dead at the end of the first year, but 48 per cent were dead within six years of the induction of artificial pneumothorax.

TABLE II.—THE MORTALITY RATES FOR THE CONTROL AND ATELECTATIC SERIES

	Controls		*Atelectasis*
	First Series of Unselected Cases	*Cases with Artificial Pneumothorax*	
No. of cases	219	100	30
Per cent. Dead:			
At one year	13	10	3
At six years	46	25	48

A study of Table II shows that at the end of six years there is a considerably higher mortality in those cases in which atelectasis occurred. This is not due to any difference in the incidence of toxicity of the two groups, as this was the same in both series. Nor is it due to the fact that there was a higher incidence of intrapleural adhesions in the atelectatic series, as this was also comparable in both groups. The only adverse factor was the occurrence of a lobar atelectasis.

It will be apparent from this study that an atelectasis of the upper lobe which persists for over three months is of serious prognostic significance. This incidence of appreciable fluid is higher in these cases and this in turn contributes to the much worse prognosis.

Summary

358 cases of artificial pneumothorax have been surveyed and 49 cases with an atelectasis of the upper lobe analysed.

The predisposing factors to atelectasis are discussed.

The incidence of fluid was 50 per cent. as compared with 16 per cent. in a control series.

The mortality rate at the end of six years was 48 per cent. in the atelectatic cases as compared with 25 per cent. in the control series.

I wish to thank Dr. I. C. Macintyre, Medical Director of Cashmere Sanatorium, for permission to publish this paper.

REFERENCES

BUTTERFIELD, D. (1949): Public Health Thesis for the Degree of M.B., Ch.B. (N.Z.).
COELLO, A. J. (1951): *J. Thor. Surg.*, **21**, 2, 135.
COELLO, A. J., and NAGLEY, M. N. (1948): *Tubercle*, XXIX, **10**, 231.
FARQUHARSON, M. (1951): *Tubercle*, XXXII, **5**, 108.
HOUGHTON, L. E. (1950): *Tubercle*, XXXI, **3**, 50.
MAHER-LOUGHNAM, G. P. (1950): *Tubercle*, XXXI, **4**, 74.
MITCHELL, R. S. (1951): *Am. Rev. Tuberc.*, **64**, 1, 1.
MITCHELL, R. S. (1951): *Am. Rev. Tuberc.*, **64**, 2, 127.

SOME UNUSUAL MANIFESTATIONS OF BRONCHIAL CARCINOMA

By Geoffrey Flavell

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The common symptoms of cancer of the lung are cough, discomfort or pain in the chest, dyspnœa, hæmoptysis, malaise and fever, wheezing and eventually loss of weight. In 60 per cent. of patients a growth is associated with pulmonary collapse; in 10 per cent. with abscess formation; and these two factors naturally play an important part in determining the symptomatology. In addition metastases which lodge in bones may produce aching and persistent pain in them, sometimes confused with "rheumatism" but localised to one or two sites; while those affecting the central nervous system result in a wide variety of neurological lesions depending upon the precise anatomical position of the secondary deposit but all having this in common, that they are essentially asymmetrical and invariably progressive.

This general symptomatology is now well known and clinicians are increasingly alert in making early diagnosis of lung growths. There are, however, two further syndromes less well known, which though in themselves rare (that is, less than 2 per cent. of the cases I have seen) yet occur with sufficient frequency among the great number of patients now suffering from lung cancer to justify description, and in addition merit discussion for their great intrinsic fascination and unsolved mystery. They are respectively pulmonary hypertrophic osteoarthropathy, which is the commoner of the two, and carcinomatous neuropathy. While quite unrelated to each other these phenomena have certain features in common: they are symmetrical; they have no connection with metastases; they are not necessarily progressive; they occur apparently quite capriciously, being associated with tiny growths or with large ones, and with neoplasms of any histology; their origin is quite unknown; and patients are often treated for long periods to relieve the symptoms they produce without the presence of a bronchial cancer being suspected. I propose, therefore, to give three recent and typical examples of each and briefly to discuss them.

I. Pulmonary Hypertrophic Osteoarthropathy

It is an extraordinary thing that we should remain so ignorant of a condition first described by Hippocrates in the fifth century B.C.; but, as West aptly remarked in 1897, "clubbing is one of those phenomena with which we are all so familiar that we appear to know more about it than we really do." An enormous and quite inconclusive literature exists upon the subject, and at least a dozen different theories, none wholly reconcilable with the known facts, have been advanced to account for it. Mendlowitz, who sum-

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marised and discussed them fully in 1942, has described them as "a welter of hypothesis."

"Clubbing" is characterised by an increase of all the tissues of the finger tips, and though this increase is most apparent in the fibro-elastic tissue of the nail bed it can also be seen in the fatty connective tissue of the ball. There is dilatation of the smaller blood-vessels and increased thickness of their walls as well as the formation of new capillaries. The new subperiosteal bone deposition is best seen in relation to the peripheral epiphyses of the long bones and at the muscular insertions to their shafts. Accompanying these changes is a tendency to osteoporosis of cancellous bone. In short, the observable tissue changes are best explained by an increased peripheral blood flow causing "overnutrition" of the parts. Abolition of arthralgia has been described in a few cases in which the growth itself was not removed but the pulmonary artery was alone ligated (Wyburn-Mason, 1948) or the hilum of the lung denervated (Brea, 1948, and Hansen, 1951). The pain, however, is always abolished, and at once, when the neoplasm is resected. Such sudden cessation, together with the experimental facts described, make a toxic theory of causation untenable, since toxins would presumably continue to circulate at least for some time after the growth's removal, and could not be affected by hilar neurectomy, though they possibly might be by pulmonary artery ligation. An "autonomic nervous reflex" theory remains, unsupported by any direct experimental or anatomical evidence.

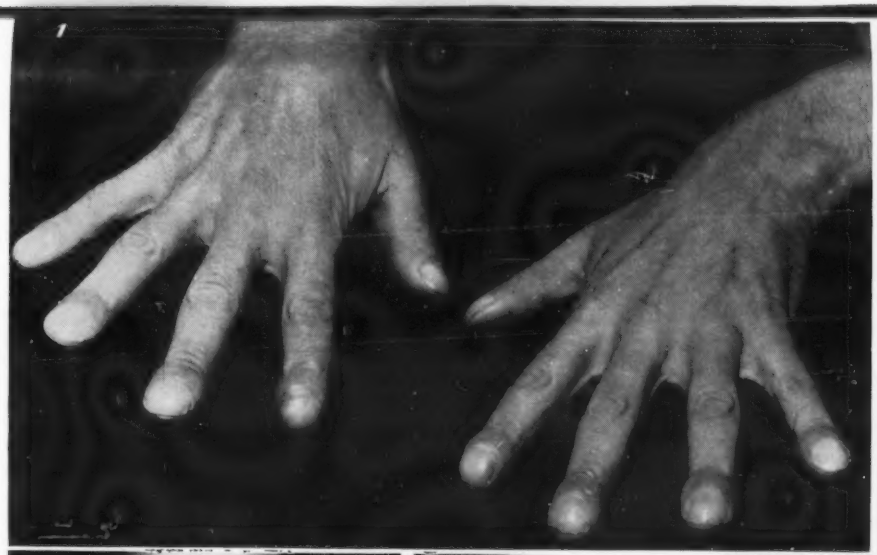
The pain resulting from hypertrophic osteoarthropathy is usually referred to the wrists, ankles, knees and elbows. It is symmetrical in distribution, aching and persistent in character, and often keeps the patient awake at night. Such patients, since they are mostly in late middle age, tend to be treated for "rheumatism" or "arthritis," and heat and other forms of physiotherapy are prescribed, sometimes for long periods. If X-rays are taken they are confined to the apparently affected joints, where osteoarthritis may actually be present, and the shafts of the long bones excluded so that the new bone deposits are missed. It is not until an hæmoptysis occurs, or some other symptom referable to the lung, that attention is turned to the chest, and by this time treatment may come too late. At the best, much valuable time has been lost.

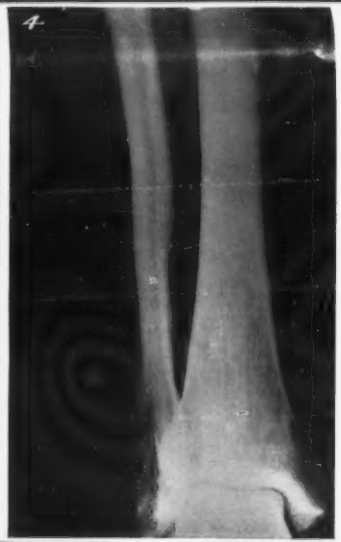
There follow three case histories typical of this condition, in two of which the growth was small and removable, while in the third the extent of the infiltration was virtually maximal, since a condition of carcinomatosis lymphangiosa existed.

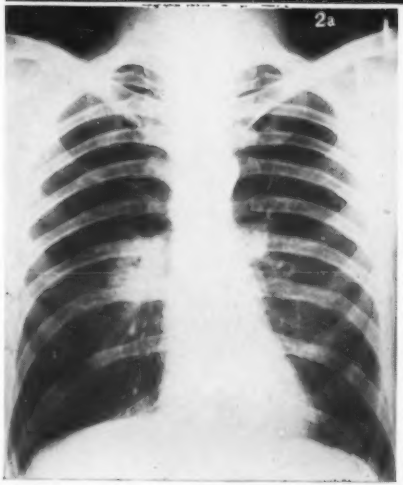
Case Histories

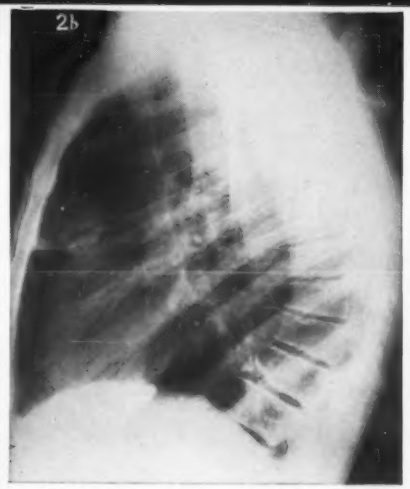
(1) A metal polisher, aged 45, exactly one year prior to admission developed joint pains, the ankles being first affected, then the knees, which became swollen as well as painful, and later aching pain spread to the hips and wrists. The condition was diagnosed as "rheumatism" and the usual treatments for this were begun, and continued for nearly a year, though without relief. The pain became constant and sleep was difficult.

He lost no weight and had no symptoms referable to his chest until a month before admission an hæmoptysis occurred. On admission there was gross clubbing of fingers (Fig. 1) and toes and slight swelling of both ankles,









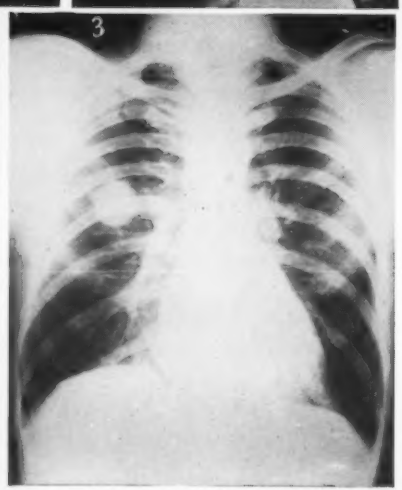


FIG. 1.—The clubbed fingers seen in Case 1.

FIGS. 2A and B.—A small cavitating carcinoma in the anterior segment of the right upper lobe (Case 1).

FIG. 3.—A discreet round lesion in the upper lobe of the right lung revealed on mass radiography (Case 2).

FIG. 4.—Subperiosteal new bone on the medial aspect of the right fibula (Case 2).

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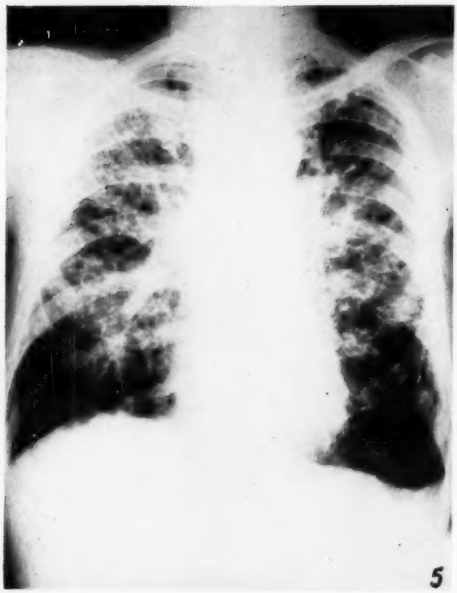


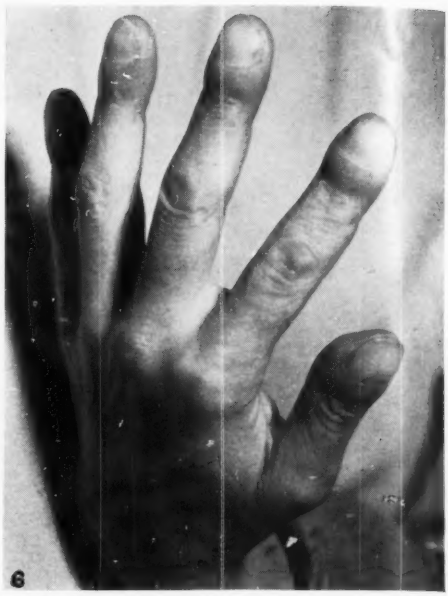
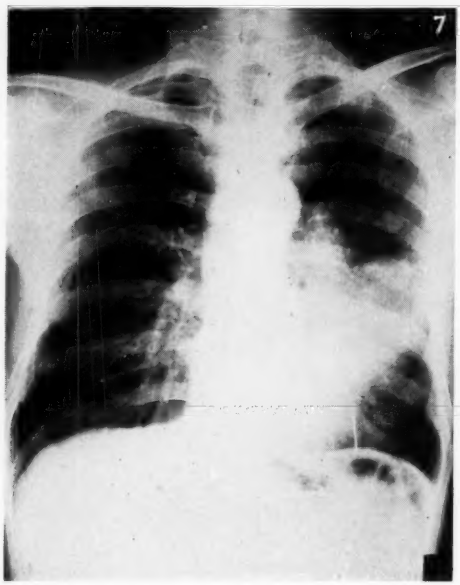


FIG. 5.—Carcinomatosis lymphangiosa seen in Case 3.

FIG. 6.—Well-marked clubbing (Case 3).



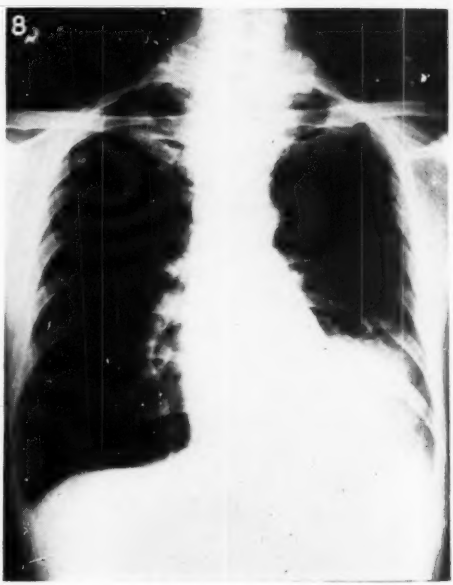


FIG. 7.—A massive bronchial carcinoma in the left lung, associated with carcinomatous neuropathy (Case 4).

FIG. 8.—An oat-celled carcinoma in the left lower lobe, whose extirpation was followed by neuropathy (Case 5).

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knees, the left elbow and the left wrist. X-rays of the limbs demonstrated subperiosteal new bone formation at the extremities of most of the long bones, in particular the upper and lower ends of radii, ulnas, tibiæ, fibulæ and lower ends of femora. X-ray of the chest showed a small cavitating opacity in the periphery of the anterior segment of the upper lobe of the right lung (Fig. 2a and 2b).

A right pneumonectomy with intrapericardial ligation of the vessels and block dissection of the mediastinal glands was carried out. The growth proved to be a columnar- and polygonal-celled carcinoma and no extension was found to any of the regional glands.

The morning after operation the patient said: "All the pain in my joints has disappeared. It is the first time for a year I have been free of it." Two days later he remarked the swelling of his fingers to be less, the red and shiny skin at the base of the nails having become crinkled and relaxed.

He has had no further pain in any joint, and the clubbing of the fingers has progressively diminished with the growth of the nails.

(2) A business man, aged 50, suffered from joint pain, chiefly in his wrists, ankles and knees, for five months and was treated for rheumatism by heat and massage. Towards the end of this period he noticed that his fingers were becoming clubbed. Soon after he attended a Mass Radiography Unit, where a circumscribed rounded opacity was discovered in the upper lobe of his right lung. He had no symptoms directly referable to his chest (Fig. 3).

A right pneumonectomy was carried out. The growth proved to be a columnar-celled adenocarcinoma and one metastasis was present in a hilar gland. X-rays of the long bones showed a fine deposition of subperiosteal new bone at the usual sites (Fig. 4). The day following his operation the joint pains vanished, and there has been no recurrence either of them or of the growth in the year that has since elapsed.

(3) A retired man aged 65 suffered from severe joint pains for some nine months and was treated for rheumatism. He latterly noticed clubbing of his fingers. In the last three months of the period he became increasingly dyspnœic and began to lose weight. X-ray of his chest showed a diffuse generalised infiltration of both lung fields spreading from a mediastinal mass (Fig. 5). No subperiosteal bone deposits could be detected radiologically, but finger clubbing was well marked (Fig. 6). He went downhill and died four months later. Carcinomatosis was present and the growth was a bronchial adenocarcinoma.

These three cases well typify the syndrome. In all, joint pains were the presenting symptom and long preceded the discovery of a growth in the lung. All had gross finger clubbing and two had well-marked radiological changes in the long bones. In spite of these changes, pain in the joints ceased immediately after the removal in both instances of small peripheral growths seemingly quite disproportionate to the symptoms resulting from them. By contrast the third, inoperable, case presented practically maximal involvement of the lung parenchyma but the bone changes were rather less than in the other two. It is of some interest that all three growths were adenocarcinomata.

II. Carcinomatous Neuropathy

At the end of the nineteenth century several German neurologists (Oppenheim, 1888; Nonne, 1900; Siefert, 1902) expressed the view that certain

neurological lesions associated with cancer might be due to a toxin arising from the growth and circulating in the blood stream. This view later became discredited when many such neuropathies were demonstrated to be due to a condition variously called "pachymeningitis carcinomatosa" or "meningitis carcinomatosa." In this palsies, pain and bladder symptoms were associated, not with blood-borne metastases in the brain and spinal cord, but with perineural lymphatic spread of malignant cells originating in many (but not all) instances from bronchial neoplasms (Craig *et al.*, Alpers and Smith, Selinsky), and resulting in diffuse infiltration of the dura or the pia arachnoid. Hassin (1922) believed that a thorough microscopical search of the nervous system would always reveal such infiltrations in these cases, even if no naked-eye abnormality existed.

In 1939 Dr. D. Kendall and, later, Professor Denny-Brown demonstrated a patient at the Royal Society of Medicine in whom peripheral polyneuritis was linked with a carcinoma of lung, but no such metastatic lesions could be demonstrated. This, together with two further instances, was first published by Wyburn-Mason in 1948, who then expressed the view that, if the lesions were not caused by intrathecal implantation of malignant cells, they must be due either to a toxic or metabolic disturbance (when they should be both symmetrical and generalised) or to some reflex phenomenon from the lungs.

In none of his three patients was there any evidence of malignant cells in the central nervous system, but all showed some degree of œdema, and hyperæmia of the dorsal root ganglia with demyelination of their fibres. Dr. Denny-Brown discussed two of these patients in greater detail and said "the most remarkable change was the severe loss of nerve cells in the dorsal root ganglia without corresponding change in the ventral roots. No trace remained of the majority of cells, their empty capsules alone marking their previous situation." He regarded the condition as a primary atrophic process affecting the nerve cells, without inflammatory or vascular reaction, and constituting "a unique example of de-afferentation in man." There was an associated degeneration of striped-muscle fibres. The condition of his two patients closely resembled experimental pantothenic acid deficiency, and in general was consistent with metabolic disorder. A number of substances such as thiopanic acid and phenyl pantothenone interfere with the biological conjugation of pantothenic acid in metabolism, and Denny-Brown thought it possible that bronchogenic carcinomas produced a substance having this effect.

In 1950 Lennox and Prichard reviewed 299 cases of carcinoma of the lung in the records of the Hammersmith Hospital in an attempt to discover further instances of associated peripheral neuritis and to determine if possible its frequency. In all, five such were found, making an incidence of 1·7 per cent., and among 600 controls there were none. A further search among 141 proved cancers of the lung in the Ministry of Pensions records revealed three patients with otherwise unexplained neuritis—an incidence of 2·1 per cent. closely agreeing with the former figure. They also found that the association of carcinoma and neuritis accounted for some 29 per cent. of the instances of polyneuritis of unknown etiology in their files.

A pneumonectomy was performed upon one of Lennox and Prichard's patients, although they state that growth was left behind at the time of operation, and no marked change in the neuritis followed. A patient whose growth was inoperable, however, showed some spontaneous improvement while in hospital.

So far, then, eleven instances of associated bronchial carcinoma and lower motor neurone disease are known, and all have proved progressive and ultimately fatal. The growths were squamous or oat-celled with about equal frequency.

In none of the patients so far described has the course of the disease been characterised by remissions, with the possible exception of that already mentioned, and in this instance the improvement does not appear to have been striking. Only one pneumonectomy has been performed and that was incomplete.

Case Histories

(4) A cellulose technician, aged 55, was admitted to the care of Sir Russell Brain. Nine months previously his feet had begun to "flap" as he walked, and shortly afterwards he noticed numbness of both calves, especially at the end of the day. The sensation, increasing to a dull ache, was made worse by exercise. Eventually he could not walk up or down stairs. After some six months the muscles of his left arm and hand wasted and grew weak, and he developed a vertical headache at first paroxysmal, later continuous. He slept little, ate poorly and lost 2 stone in weight.

On admission he was virtually bedridden, had rotatory nystagmus, bilateral ptosis, wasting of the shoulder girdle muscles and those of both arms and hands, worse on the left, with weakness and some inco-ordination. Both legs were hypotonic and wasted and there was marked weakness of all movements. In addition it soon became evident that he had a large bronchial carcinoma in his left lung (Fig. 7). I subsequently removed this, although at first it seemed likely to prove inoperable. The growth was oatcelled and mediastinal glands involved were removed. Following operation the patient declared his headache had gone and the pains in his legs were better. Within a month both arms and legs felt stronger, he was able to walk upstairs and his grip had improved. Within two months of the removal of his lung he could walk two miles at a normal pace without a stick, his feet gave no trouble and he could sit easily in a chair. He even began to work and was able to paint walls successfully. His headache and pains completely disappeared and he gained a stone in weight.

Six months after his operation a metastasis appeared on his abdominal wall, and soon afterwards all his previous disabilities returned. He went rapidly downhill and died ten months after his pneumonectomy.

At autopsy numerous metastases were found, two only of which were in the central nervous system, one (3 cm. in diameter) in the right pons, the other (2 by 1 by 1 cm.) in the left inferior frontal gyrus. Other changes were predominantly those of muscular atrophy. It is evident that the secondaries present could not have produced his neurological symptoms.

The improvement in this patient following pneumonectomy was striking and began very soon after operation. Subjectively he was emphatic about his relief from pain within a few days, and objectively the return of muscular

strength and co-ordination was equally definite within a few weeks, until, hitherto bedridden, he was able without difficulty to climb a flight of stairs. Such an amelioration may have been due simply to a remission of the polyneuritis and unrelated to the removal of the lung, being merely coincidental with it, and coincidental in its worsening with the spread of secondary deposits. However, no such dramatic and sustained remission has so far been reported among the other cases known.

It is hardly possible for such a recovery to take place had the polyneuritic symptoms been caused by implanted malignant cells, however diffuse and elusive they might be.

(5) A publican, aged 51, had ten weeks' history of pain in the left chest with fever, soon followed by cough, dyspnœa and loss of weight. He had no neurological symptoms. An oatcelled carcinoma of the left lung (Fig. 8) was diagnosed and resection carried out. Secondary deposits were found in two mediastinal glands removed *en bloc* with the lung. He made an uninterrupted recovery from his operation and returned to work.

Exactly a year later he began to lose weight and complained of weakness in his legs. In view of the nature of his original growth metastatic spread was assumed. Difficulty in walking increased and in six months he lost 2 stone in weight. Weakness was present in both legs, the left becoming almost flail-like, and he had difficulty in standing upright. The weakness later involved both shoulders. It was accompanied by symmetrical wasting of the shoulder girdle muscles, of the gluteii and of the hamstrings, but no sensory changes.

At this stage he was readmitted to hospital under the care of Dr. Ronald Henson as a case of carcinomatous neuropathy. Dr. Henson carried out very full investigations but without significant positive findings. There was no trace of secondary deposits.

For some time after this his neuropathy remained *in statu quo*, but he returned to work. Six months ago his weight began to increase and he has now almost regained his whole loss. He feels better in himself, his appetite is returning, he is able to do much more work than formerly, and though there is still weakness in both thighs there is a distinct improvement in his neuropathy. Nearly three years have elapsed since his operation without evidence of recurrence.

(6) A labourer, aged 59, five months before admission first noticed aching pain in both calves, constant and worse on walking. Shortly afterwards his legs became weak and he could walk only with difficulty, dragging his feet. A few days later still sensation in the feet was lost and he could not feel himself walking. The numbness and weakness got worse, spreading up the legs to the thighs. The following month he lost his sense of touch and could not feel objects picked up. Weakness developed in his fingers and hands.

Three months after the onset of these severe neurological symptoms cough and dyspnœa supervened, but as they did so, preceded by pins and needles in the toes and feet, there began a distinct recovery both of weakness and sensation.

On examination a massive oatcelled carcinoma was found in the left lung. Neurologically there were the following positive findings: slight bilateral wasting of dorsal interossei; bilateral dropped feet with wasted and tender calf muscles; ankle jerks were absent, and there was some sensory loss in both feet and legs. The C.S.F. was normal and W.R. negative. On thoracotomy the growth was found to be inoperable, but although the patient got worse the neurological symptoms continued to improve.

These are three among eight representative cases of neuropathy associated with carcinoma which have been under my care in the past two years and they provide an intriguing contrast: in one a remarkable remission coincided with extirpation of the growth; in another the neuropathy was almost better before the growth was attacked; and in the third it appeared almost a year after operation and does not seem to be associated with metastases. In some instances symptoms are predominantly motor, almost myasthenic; in others sensory and resembling peripheral polyneuritis, or a mixture of the two. Such symptoms may long precede any referable to the chest, and no relation exists between the size or histological type of the growths and their severity. It seems likely in view of such case histories that reversible changes in the nervous system or motor end plates must precede actual degeneration as detailed by Denny-Brown, and there can be no doubt that patients with unexplained peripheral neuritis, atypical myasthenia or disseminated sclerosis should always have their chests X-rayed.

REFERENCES TO HYPERTROPHIC OSTEOARTHROPATHY

ALVAREZ, G. H. (1948): *Rev. de la Asociación Méd. Argentina*, **62**, 690.
BAMBERGER, E. von (1889): *Wien. Klin. Wchnschr.*, **2**, 226.
BREA, M. M. (1948): Discussion with Pavlovsky, cited *Year Book of General Surgery*, p. 306.
HANSEN, J. L. (1951): Personal Communication.
MENDLOWITZ, M. (1942): *Medicine*, **21**, 269.
MENDLOWITZ, M., and LESLIE, A. (1941): *Amer. J. Pathol.*, **17**, 458.
WEST, S. (1897): *Trans. Clin. Soc. London*, **30**, 60.
WYBURN-MASON, R. (1948): *Lancet*, **1**, 203.

REFERENCES TO CARCINOMATOUS NEUROPATHY

ALPERS, B. J., and SMITH, O. N. (1920): *Amer. J. Cancer*, **32**, 361.
BARNES, S. (1905): *Brain*, **28**, 30.
CORNWALL, L. H. (1927): *Arch. Neurol. Psychiat.*, **17**, 466.
CRAIG, W. M., WOLTMAN, H. W., and KERNOHAN, J. W. (1939): *Amer. J. Cancer*, **36**, 12.
DENNY-BROWN, D. (1948): *J. Neurol. Neurosurgery and Psychiat.*, **11**, 73.
DOSTROVSKY, A., and SAGHER, F. (1946): *Brit. J. Derm. Syph.*, **58**, 52.
FRIED, B. M. (1925): *Arch. Intern. Med.*, **35**, 1.
GLOBUS, J. H., and SELINSKY, H. (1927): *Arch. Neurol. Psychiat.*, **17**, 481.
HASSIN, G. B. (1919): *Arch. Neurol. Psychiat.*, **1**, 705.
HASSIN, G. B., and SINGER, H. D. (1922): *Arch. Neurol. Psychiat.*, **8**, 155.
LEIGH, A. D., and MEYER, A. (1949): *J. Neurol. Neurosurg. Psychiat.*, **12**, 287.
LENNOX, B., and PRICHARD, S. (1950): *Q. J. Med.*, **19**, 74.
MCCOMBS, R. P., and MACMAHON, H. E. (1947): *Med. Clin. N. Amer.*, **31**, 1148.
SELINSKY, H. (1930): *Arch. Neurol. Psychiat.*, **23**, 197.
WINTROBE, M. M., FOLLIS, R. H., STEIN, H. J., MUSKATT, C., and HUMPHREYS, S. (1942): *J. Nutrit.*, **24**, 345.
WINTROBE, M. M., MILLER, J. L., and LISCO, H. (1940): *Bull. Johns Hopk. Hosp.*, **67**, 377.
WYBURN-MASON, R. (1948): *Lancet*, **1**, 203.

PROBLEMS OF DIAGNOSIS IN INTRATHORACIC DISEASE

THREE CHEST CASES

By G. E. Beaumont and D. Geraint James
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The three chest cases which are described in the following article have no direct connection with one another. They have been selected, however, with the hope that they may prove of interest to the reader by illustrating certain well-recognised and fundamental principles in the art and science of medicine.

The first case is based on the familiar aphorism "Experience is fallacious and judgment difficult," and underlines the danger of giving a definite prognosis, even in cancer. Although the diagnosis of this fatal disease was made by biopsy, yet a favourable result was obtained by hormone therapy alone.

The second illustration emphasises that an operative procedure, devised to establish a diagnosis, may be an act of supererogation if the disease, when left to nature, cures itself.

The third case exemplifies the application of physiological knowledge to clinical medicine. It indicates how the effect of pregnancy upon the activities of the pituitary and adrenal glands can be demonstrated by observing an experiment made by nature—an experiment, moreover, which rivals those devised by modern research workers. The increased production of cortisone during pregnancy, and the subsequent fall to normal levels, are reflected in the X-ray appearances of the lungs in a case of sarcoidosis.

Case 1

Miss G. N. was a 41-year-old elocution teacher and had a right radical mastectomy for a spheroidal-cell carcinoma of the breast in 1934. She remained well until July 1948 when she developed an attack of bronchitis, with dyspnœa and pleural pain in the left lower chest. This recurred in February 1949, with increasing dyspnœa, and she also complained of pain in the tip of the left shoulder. The physical signs indicated a large left pleural effusion, and this was confirmed radiologically (Fig. 1). Aspiration produced 22 oz. of dark brown, slightly turbid fluid. Two days later a further 50 oz. of brown fluid was aspirated, and on this occasion 950 ml. air was introduced to replace the fluid. A chest radiograph now showed a left hydropneumothorax with numerous oval pleural deposits (Fig. 2). These deposits were suggestive of pleural metastases. This suggestion was strengthened when a thoracoscopy was performed, in which it was reported that "opacities characteristic of secondary deposits were seen." Biopsy of such a deposit revealed a carcinoma, largely undifferentiated, but with some attempt at tubule formation (Fig. 3).

It seemed probable that these metastases were either a very late sequel, fifteen years after the breast carcinoma, or they were due to a second primary carcinoma, possibly in the bronchus. Despite such a grave diagnosis, the

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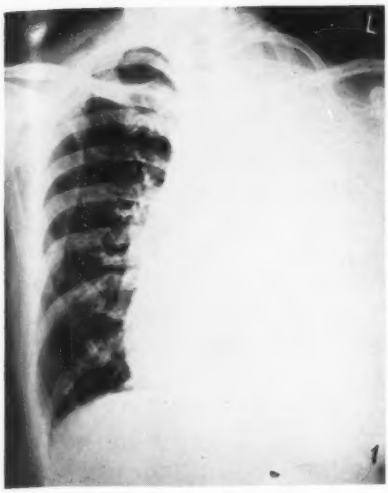
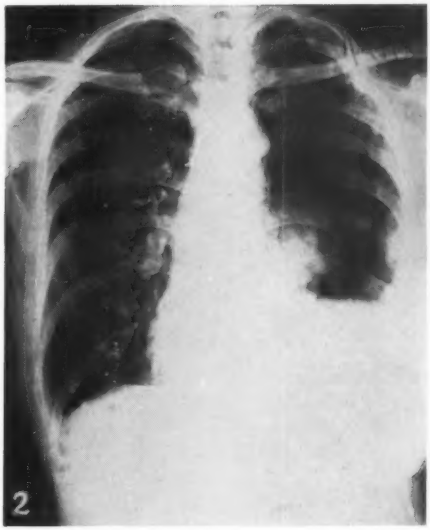




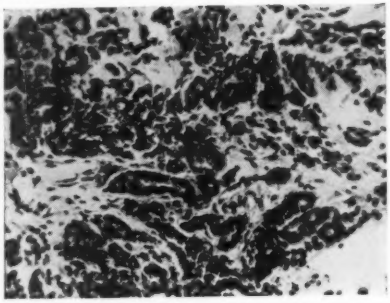


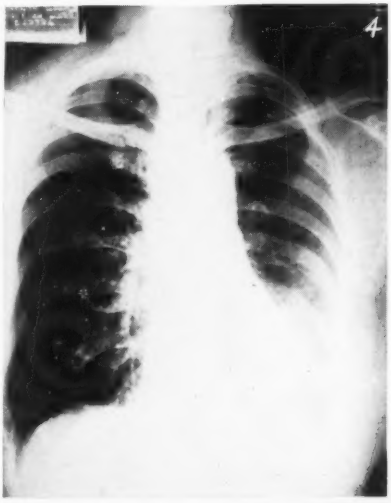
FIG. 1.—Case 1. Chest radiograph showing large left pleural effusion.

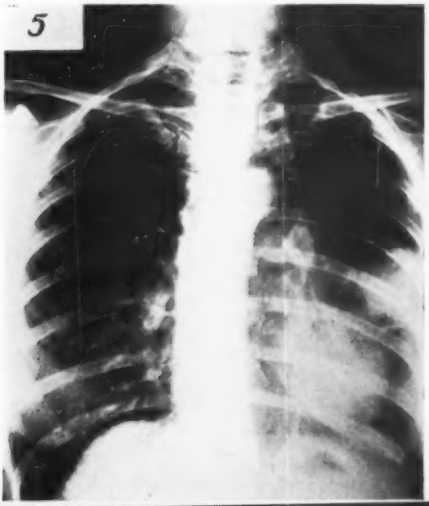
FIG. 2.—Case 1, after chest aspiration, showing left hydropneumothorax with numerous oval pleural deposits.

FIG. 3.—Case 1. Photomicrograph of pleural biopsy, showing largely undifferentiated carcinoma, but with some attempt at tubule formation. ×275.

FIG. 4.—Case 1. Chest radiograph, two years later, showing only residual pleural thickening at left base.

FIG. 5.—Case 2. Penetrating chest radiograph showing area of consolidation in anterior segment and lingula of left upper lobe, with adjacent enlarged hilar gland.





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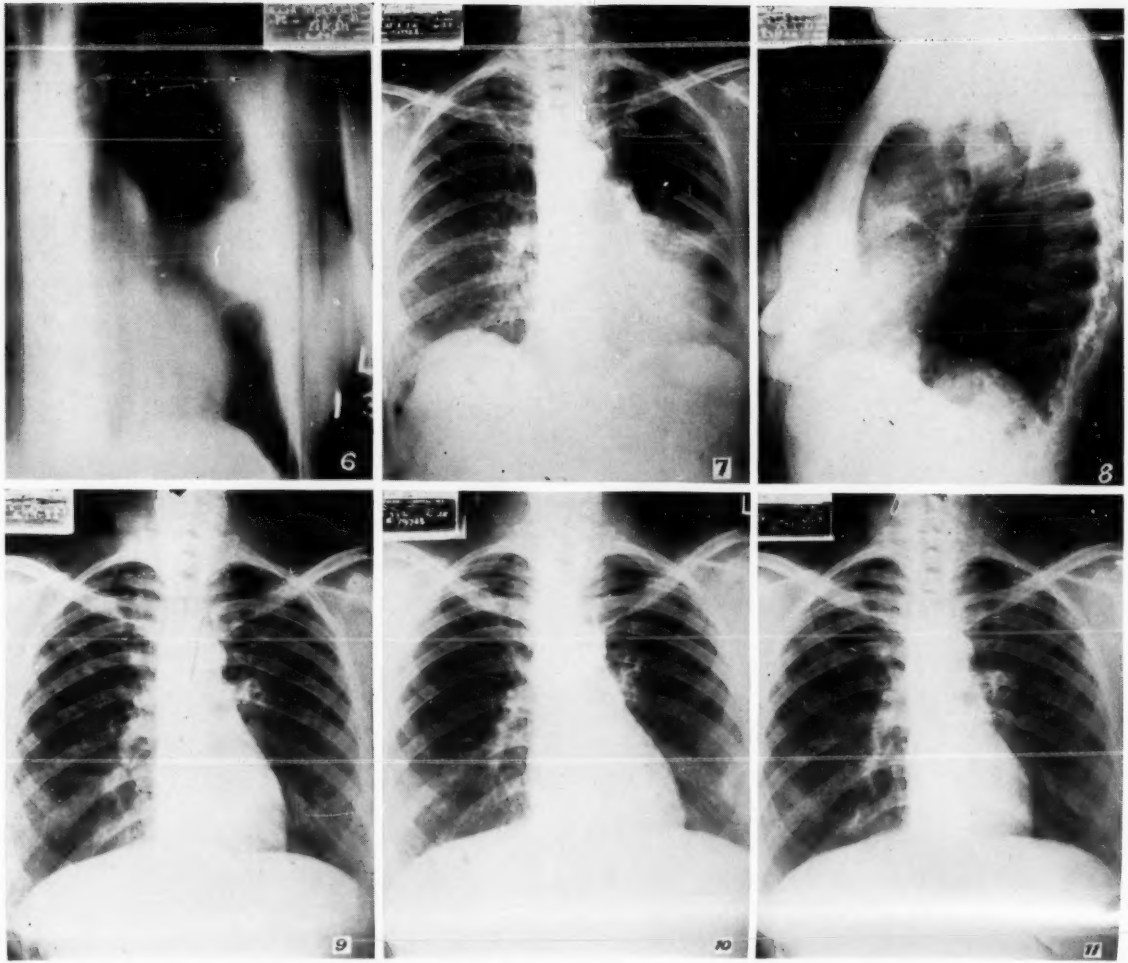

FIG. 6.—Case 2. Tomogram, 13 cm. cut, outlining opacity seen in Fig. 5.

FIG. 7.—Case 2. Chest radiograph, 3 months after Fig. 5, showing some residual fibrosis.

FIG. 8.—Case 2. Left lateral view, accompanying Fig. 7.

FIG. 9.—Case 3. Diffuse reticulation both lung fields. First month of pregnancy.

FIG. 10.—Case 3. Ninth month of pregnancy. Complete clearing of pulmonary reticulation. Basal markings due to heavy breast shadows.

FIG. 11.—Case 3. Two months after delivery. Return of bilateral pulmonary reticulation.

patient herself now felt much better, since the fluid had been removed from her chest.

She was treated by intramuscular injections of testosterone propionate, 100 mg. daily for six weeks, at home, but because of increasing hirsutism she discontinued this treatment.

A little over two years later she returned to the out-patient department for a reassessment of her general health. She was healthy-looking, had gained over 1 stone in weight, and felt well, apart from occasional backache when tired. During the two years following the testosterone treatment she had led a useful life, doing a full-time clerical job.

Apart from some pleural thickening at the left base the chest radiograph was clear. There was no evidence of pleural metastases (Fig. 4).

Since that first return visit she has remained in good health and continues to pursue an active and full life four years after the malignant left pleural effusion was first diagnosed.

CASE 2

Miss A. H., a 57-year-old civil servant, developed a left-sided pneumonia with pleurisy in January 1952. It was associated with a cough, purulent sputum and a pyrexia of 100°-104° F. She was unrelieved by a course of sulphamezathine to a total of 20 gm. and followed by penicillin 400,000 units daily for four days. In view of this lack of response to chemotherapy a portable chest radiograph was arranged. It revealed consolidation in the anterior segment of the left upper lobe. She was told that she had a virus pneumonia, and so was given a course of chloramphenicol, 2 gm. daily for 6 days. The pyrexia gradually subsided and the cough and purulent sputum settled, but a second chest radiograph showed no radiological improvement. A further course of chloramphenicol was started, but a drug rash developed and so this treatment was abandoned. She was then admitted to hospital for further investigation.

On admission she appeared tired and drawn, but complained of very few symptoms. She had a slight dry cough, and occasional pain in the left lower chest on deep inspiration. She was afebrile, but there were signs of consolidation of the lung in the left axilla and at the left base posteriorly. Chest radiographs demonstrated that the heart was displaced to the left side, and an opacity was situated in the region of the anterior segment and lingula of the left upper lobe, with an adjacent enlarged left hilar gland (Figs. 5 and 6). The appearances were suggestive of a carcinoma of the bronchus and a bronchoscopy was performed. The left main bronchus appeared rigid and acutely curved, so that it was impossible to pass the bronchoscope down to the orifice of the left upper lobe. There was narrowing beyond this point, from which a blind biopsy was taken. This biopsy showed desquamated epithelial cells only. Despite this negative biopsy, a thoracotomy was suggested in view of the strong suspicion of carcinoma of the left bronchus.

The patient refused surgery and instead went abroad. She consulted, in turn, chest specialists in Switzerland and Paris, and on each occasion was advised to undergo a thoracotomy, because of the likelihood of a malignant neoplasm. However, these specialists were handicapped because they were assessing the condition on the strength of single chest films. When she returned to Britain, three months later, a chest radiograph showed that the opacity was now smaller, and it has continued to decrease in size (Figs. 7 and 8). One year after the onset of her pneumonia, she is in good health and is holding a responsible job in the Civil Service.

It seems probable that she is recovering from a simple lung abscess which has gradually and slowly absorbed, without surgical intervention.

CASE 3

Mrs. M. L. was a 24-year-old nurse when she first complained of a slight productive cough in 1948. She appeared healthy, and there were no abnormal physical signs to be found. A chest radiograph revealed bilateral enlargement of the hilar glands.

From 1940 to 1947 she had been a Red Cross nurse in Sweden, where she received B.C.G. vaccination in 1944. Because Mantoux conversion did not occur on the first occasion, this was repeated and her Mantoux reaction finally became positive. At this time, and again in 1946, there was no radiological evidence of hilar lymphadenopathy.

During 1949 a Mantoux test in a dilution of 1 : 10,000 was negative, but was reported as positive in a dilution of 1 : 100. At this time tubercle bacilli could not be found in the sputum, but her erythrocyte sedimentation rate was 20 mm./hour, Westergren method. Sarcoidosis was considered as a cause of the hilar adenopathy, but there was no confirmatory evidence of this disease elsewhere. Other glands were not enlarged, and there were no cysts demonstrable in X-rays of hands and feet.

Since 1949 she has remained well, apart from a slight dry cough. However, serial chest radiographs since that time have revealed gradually increasing diffuse reticulation of both lung fields. Simultaneously with this pulmonary involvement the hilar lymph glands have gradually become smaller.

In 1950 a pregnancy was considered inadvisable and was terminated. In January 1952 she again became pregnant, and was admitted to hospital for assessment to decide whether she should continue with it in view of the pulmonary reticulation. On this occasion a chest radiograph showed diffuse reticulation of both lung fields (Fig. 9) and a Mantoux reaction was negative to a dilution of 1 : 100. The blood count was normal and she had a Westergren erythrocyte sedimentation rate of 15 mm. hour. A Kveim test for sarcoidosis was negative. Despite this negative result, sarcoidosis seemed the most likely diagnosis, although no histological proof of such a lesion was obtainable.

Because of the patient's good general condition, and the fact that adrenal corticoid hormones have been usefully employed in the treatment of sarcoidosis, it was decided to allow pregnancy to continue. It was felt that the increased endogenous production of adrenal cortical hormones in pregnancy might benefit her pulmonary condition. The patient was eager to continue with this pregnancy.

Whether the pregnancy had any influence or none is difficult to assess, but radiologically pulmonary reticulation gradually disappeared. At the time of labour a chest radiograph showed no abnormality (Fig. 10).

Two months after the baby was born a chest radiograph again showed diffuse reticulation of both lung fields (Fig. 11). This return of the reticulation certainly seemed to underline the association of pregnancy and clearing of the lung fields radiologically. It is tempting to suggest that it was a return of the sarcoidosis after withdrawal of the increased endogenous adrenal corticoids.

BRONCHIAL CARCINOMA IN DUSTY OCCUPATIONS

OBSERVATIONS IN BOILER SCALERS AND GRAIN DOCKERS

By Lasar Dunner and M. Sanger Hicks

From the Chest Clinic, Hull

The incidence of bronchial carcinoma has been increasing during the last thirty years and at an accelerated rate in the last decade. Considerable speculation has arisen concerning the causes of this rising morbidity and the etiology of bronchial carcinoma in general. The fumes of heavy fuel oils and tar products associated with road dust, as well as cigarette smoke, have all been implicated. If the inhalation of dust is indeed an etiological factor, one would expect to find bronchial carcinoma developing in men working in dusty industries. Such findings have been recorded. Rostoski (clinically) and Schmorl (pathologically) (1928) described the occurrence of cancer in conjunction with pneumoconiosis in Schneeberg miners. Schmorl frequently found cicatrices in the bronchial walls formed by the healing of so-called "pigment perforations," and considered that they were precancerous. An exogenous factor was thought to be necessary—*i.e.*, arsenical dust and/or radiation from traces of radium in the rock. Such a supposition may have been correct in their cases, but it would not be right to generalise and to attribute bronchial carcinoma to these factors alone. In connection with this idea of an exogenous factor acting upon a susceptible lung, the recent interesting work of Raeburn is worth mentioning. He performed careful histological sections on 440 lungs and found five primary growths in the peripheral bronchi without secondary metastases. He suggests that such foci in small bronchi distorted by chronic inflammation would be most susceptible to the action of an exogenous carcinogen.

In the 1947 Annual Report of the Chief Inspector of Factories, 31 cases of bronchial carcinoma out of 235 cases of asbestosis are recorded (an incidence of 13·2 per cent.). Nordmann found the incidence of carcinoma in workers suffering from asbestosis to be 17 per cent.; Wood and Gloyne found a 20 per cent. incidence. These figures appear to be significant, but those for other occupations are not so impressive. The same Report states that 91 cases of bronchial carcinoma were found among 6,884 cases of silicosis examined post mortem, a percentage of only 1·32. Vorwald and Karr (1938) reviewed the literature of 444 post mortem findings in individuals exposed to various dusts, of whom 6 had pulmonary carcinoma, a percentage of 1·3. They themselves performed post mortem examinations in 178 men exposed to a variety of industrial dusts—of whom 136 had silicosis—but found only 2 cases of carcinoma of the lung (1·12 per cent.). Siderosis has also been implicated. Kennaway and Kennaway (1936) reported an incidence of pulmonary malignancy in metal grinders two and a quarter times that of the general population. Saupe examined the lungs of 40 arsenic ore smelters

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in Freiburg (Saxonia) and found 12 cases of mild pneumoconiosis of whom 2 developed carcinoma. Inhalation of chromate dust and fumes has also been regarded as carcinogenic. Baetjer (1950), reviewing the literature in 1950, reported that 122 cases of lung cancer had been recorded among workers exposed to chromium compounds. Most cases were reported from Germany (by Koelsch, Gross, Alwens, Jonas) and the U.S.A. (by Mackle, Gregorius and Baetjer). Lung cancers have also been reported in nickel workers (Baader, 1932; Bridge, 1936). Both chromate and nickel workers suffer from allergic conditions, including bronchitis and asthma. The degenerative and proliferative cellular manifestations associated with allergy have been alleged to be potentially carcinogenic.

The present paper is a report on 26 cases of bronchial carcinoma in (*a*) dockers handling grain, seeds and other dusty cargoes and in (*b*) boiler scalers. Pneumoconiosis has been found in men working in both these trades and has been described elsewhere. All our cases were referred by their general practitioners for investigation of chest symptoms and they therefore form a selected group. As we have not had an opportunity for routine examinations of all the men in these two occupations a statistical analysis is not feasible. However, a general impression may be gained from an account of the cases with positive findings. Among grain dockers we have seen 80 cases of pulmonary tuberculosis, 35 cases of pneumoconiosis and 20 of bronchial carcinoma. Among boiler scalers there were 17 cases of pneumoconiosis, 4 of pulmonary tuberculosis and 5 of bronchial cancer. We have seen in addition one man with bronchial cancer who has worked, at different times, in both occupations concerned.

For the main facts concerning these cases reference should be made to the accompanying table. In all but two the clinical and radiological diagnosis of bronchial carcinoma was confirmed by bronchoscopy and/or pathological examination of the lung after death or operation. Of the twelve pathological examinations done only 9 were also examined for specific evidence of pneumoconiosis. With the exception of one boiler scaler (who showed obvious silicosis) there was no *radiological* evidence of pneumoconiosis in any of the other men. Nevertheless, histological evidence of slight pneumoconiosis was found in 5 cases (2 boiler scalers and 3 dockers).

Two main questions require discussion:

(1) Is there in fact a high incidence of bronchial carcinoma in grain dockers and boiler scalers?

At first sight the figures are rather striking and might suggest an undue frequency of the condition in these occupations. However, most of our cases (namely 14) were seen in 1951-52, at a time when bronchial carcinoma was recorded in increasing numbers among the general population in Hull. The total deaths from bronchial carcinoma in the city of Hull were:

1948	94
1949	94
1950	102
1951	123
1952	139

Case	Occupation	Date Diagnosed	Age	Length of Exposure (Years)	Interval ceasing Work to Diagnosis (Years)	Diagnosis confirmed by	P.M. Findings	Smoking Habits (Daily)
1	Grain docker	January 46	62	5	40	P.M.	—	2 oz. wk.
2	,,	May 46	36	17	nil	P.M.	—	35 cigs.
3	,,	November 46	48	21	16	P.M.	Slight pneumoconiosis	20 cigs.
4	,,	March 47	55	11	14	P.M.	Slight pneumoconiosis	—
5	,,	February 49	53	19	20	P.M.	No pneumoconiosis	15 cigs.
6	,,	May 49	52	5	5	P.M.	Slight pneumoconiosis	10 cigs.
7	,,	January 50	42	14	11	Bronchoscopy	—	25 cigs.
8	,,	May 50	54	7	nil	P.M.	—	20 cigs.
9	,,	April 51	63	27	nil	Bronchoscopy	—	—
10	,,	May 51	67	30	2	P.M.	No pneumoconiosis	10 cigs.
11	,,	May 51	43	25	nil	Bronchoscopy	—	12 cigs.
12	,,	June 51	45	26	nil	Bronchoscopy and operation	—	20 cigs.
13	,,	December 51	48	15	13	Operation	No pneumoconiosis in resected lung	20 cigs.
14	,,	January 52	51	33	nil	Bronchoscopy	—	1½ oz. wk.
15	,,	February 52	53	10	28	Bronchoscopy	—	15 cigs.
16	,,	February 52	50	6	27	—	—	20 cigs.
17	,,	March 52	58	40	nil	Thoracotomy	—	10 cigs.
18	,,	October 52	67	13	nil	Bronchoscopy and operation	—	20 cigs.
19	,,	October 52	62	44	nil	Bronchoscopy and operation	—	20 cigs.
20	,,	November 52	62	7	25	Bronchoscopy	—	10 cigs.
21	Boiler scaler	March 44	61	47	nil	P.M.	Silicosis	—
22	,,	March 46	46	5	nil	P.M.	Slight pneumoconiosis	10 cigs.
23	,,	May 48	47	35	nil	P.M.	Pneumoconiosis	10 cigs.
24	,,	October 50	51	7	13	Bronchoscopy	—	50 cigs.
25	,,	May 52	41	4	nil	Bronchoscopy	—	25 cigs.
26	Boiler scaler and grain worker	June 52	46	5 10	nil 14	Not bronchoscoped	—	10 cigs.

Although these figures concern a record of deaths, whereas our table records the cases when diagnosed, a comparison of the two groups seems reasonable. It might be claimed that a statistical record of deaths gives a true image of the incidence of bronchial carcinoma in the general population and that every death is covered by it. Our cases which ended fatally are supposed to be included in these figures. One cannot be certain that every docker and boiler scaler suffering from bronchial carcinoma was seen in our clinic. It is quite possible that some were seen at other clinics and hospitals in the area. If that is so, the incidence of bronchial carcinoma in dockers and boiler-scalers would be higher than our figures indicate.

These considerations may suggest that our observations are merely a reflection of the general trend towards increasing cancer morbidity, showing a peak in the last two years. There are, however, several other points which cast some doubt on such a conclusion: of the 5,000 or so dockers in Hull only about 2,500 are exposed to grain and other dusty cargoes. It is a remarkable fact that we have not seen any cases of carcinoma in the other 2,500 dockers not exposed to dust. As we have seen at our clinic an increasing number of bronchial carcinoma cases in the general population, we might have expected by the law of averages to have seen at least one or two cases among such dockers. The fact that all were confined to the group of dockers with dusty hazard would seem to suggest that dust exposure is an etiological factor. However, the dusty conditions cannot explain the recent considerable increase of cancer among the grain dockers, because these conditions have existed for a long time and remain unchanged.

Such a critical approach does not, of course, exclude the possibility that the dust concerned may produce, or at least be a factor in the development of, cancer in our cases. An etiological relationship has been alleged by many authors to occur in various dusty trades, as already mentioned in the introduction. Their findings are particularly significant as they were recorded at a time when the general cancer incidence had not reached its present high peak. The recent additional increase of carcinoma among grain dockers cannot, however, be attributed to the dust factor alone. Presumably the as yet unknown factor responsible for the increase of carcinoma in the general population is also responsible for the recent increase of bronchial carcinoma among the dockers. Another aspect concerns the relationship between pneumoconiosis and carcinoma. In keeping with other reports Professor Gough of Cardiff has found histological evidence of slight pneumoconiosis in 5 of our cases. But these findings do not imply that pneumoconiosis is an essential factor. Furthermore, neither the chemical action of silica nor the pneumoconiotic changes in the lungs can be assumed to be carcinogenic. If they were, the incidence of bronchial carcinoma in coal miners, who constitute the largest industrial group developing pneumoconiosis, would be much higher.

(2) Is there a causative relationship between cancer and cigarette smoking in our cases?

Such a relationship has been claimed generally in recent years. It would be wrong to draw any conclusions based upon such a small number of cases,

and we would therefore only record the following facts: (*a*) none of the men in this series was a non-smoker; (*b*) with one exception none of these men was a heavy smoker.

Summary

Bronchial carcinoma has been found by many investigators to be unduly frequent in certain dusty occupations. In conformity with their findings our own observations record the occurrence of bronchial carcinoma in the dusty occupations of boiler scalers and particularly in grain dockers.

There is no adequate explanation for the most recent striking increase in bronchial carcinoma incidence in grain dockers, an increase which has also occurred among the general population and the cause of which remains unsolved.

Our observations do not justify any claim in favour of or against cigarette smoking as an etiological factor.

We wish to express our thanks to Prof. Gough of Cardiff for his reports regarding pneumoconiosis in the specimens we sent him.

ADDENDUM

Since writing this paper we have seen four more cases of bronchial carcinoma in grain dockers, and also four cases in another dusty occupation, namely ships' repairers. A report on the investigation of lung damage in this latter industrial group will be published shortly.

REFERENCES

Annual Report, H.M. Chief Inspector of Factories (1947. H.M.S.O.).
Baetjer, A. M. (1950): *Arch. Indust. Hyg. and Occup. Med.*, **2**, 487 and 505.
Dunner, L. (1949): *Brit. J. Radiol.*, **22**, 264.
Dunner, L., Hermon, R., and Bagnall, D. J. T. (1946): *Brit. J. Radiol.*, **19**, 228.
Dunner, L., Hicks, M. Sanger, and Bagnall, D. J. T. (1952): *Brit. J. Tuberc.*, **46**, 43.
Hueper, W. C. (1942): "Occupational Tumours and Allied Diseases," Springfield, Ill.
Kennaway, N. M., and Kennaway, E. L. (1936): *J. Hyg.*, **36**, 236.
Koelsch, F. (1936), quoted by Hueper.
Nordmann, M. (1939), quoted by Hueper.
Raeburn, C. (1951): *Lancet*, **2**, 474.
Rostoski and Schmorl (1928): International Conference on Cancer, London.
Vorwald, A. J., and Karr, J. W. (1938): *Amer. J. Path.*, **14**, 49.
Wood, W. B., and Gloyne, S. R. (1934): *Lancet*, **2**, 251.

DANGERS OF CHEMOTHERAPY IN PULMONARY TUBERCULOSIS

REPORT OF A CASE OF ACQUIRED HYPERSENSITIVITY TO STREPTOMYCIN AND PARA-AMINO-SALICYLIC-ACID (P.A.S.)

By J. K. McKechnie

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A large proportion of persons suffering from pulmonary tuberculosis receive chemotherapy in the form of streptomycin and P.A.S. at some stage in the sanatorium treatment of their disease. Bignall (1952) has recently reviewed the current views on chemotherapy in pulmonary tuberculosis and states that its value depends on three factors—*i.e.*, bacterial resistance, the toxicity of therapeutic doses and the specific nature of the disease. Julian (1952) has reported a case treated with streptomycin and P.A.S. in which acquired hypersensitivity to both these drugs appeared simultaneously. In his case report the patient did not develop jaundice, which is known to be one of the complications of P.A.S. therapy, but abnormal liver function tests were produced. The following case is presented as an example of simultaneous development of hypersensitivity to streptomycin and P.A.S., with jaundice and profound liver dysfunction.

Case Report

The patient, P. J. R., male, aged 44, was admitted to hospital on March 25 with an anorectal abscess. This was treated surgically and no acid-fast bacilli were seen in the pus. A chest X-ray at the time of operation revealed pulmonary tuberculosis and the sputum was positive for tuberculosis. The anorectal wound was treated by the application of 1 per cent. streptomycin dressings applied twice daily, and healing occurred satisfactorily. On May 24 the patient was discharged from hospital, and while awaiting a sanatorium vacancy he was given a total of 150 G. of P.A.S. (12·5 daily).

The patient was admitted to King George V Hospital for Diseases of the Chest on June 28. He was asymptomatic and a chest X-ray on admission showed bilateral "soft" apical shadowing. The E.S.R. was 36 mm. in one hour (Westergren). The sputum contained *M. tuberculosis* on direct and cultural examination. Streptomycin 1 G. daily and P.A.S. 20 G. daily were started on July 8.

On August 2 the patient suddenly became febrile with a temperature of 102° F. On the following day a non-pruritic petechial eruption appeared on the trunk, face and limbs. High-pitched rhonchi were noted in both lung fields, and as an allergic cause for these signs and symptoms was suspected "Anthisan" 100 mgm. and ephedrine ½ gr. four-hourly were prescribed. On August 4 the rash was erythematous on the trunk and maculo-papulo-petechial on the legs and arms. The patient complained of a subjective sensation of food sticking in the back of his throat and slight relief was obtained following injection of 5 minims adrenalin. The streptomycin and P.A.S. were discontinued. A total dosage of 28 G. streptomycin and 560 G. P.A.S. had been given

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up to that time. The "Anthisan" was stopped and "Benadryl" 100 mgm. thrice daily was started.

On August 5 the patient was still febrile and the rash had faded on the trunk. An impetigenous condition was present on the face and ung. quinolor was prescribed for this. The patient's general condition otherwise was good. On the following day the eruption on the face was slightly worse and small white ulcers were noted on the buccal, faucial and sublingular mucosa. A blood count at this time showed a white cell count of 27,000. The differential count was 49·5 per cent. polymorphonuclear cells, 16 per cent. lymphocytes, 2·5 per cent. monocytes, 31 per cent. eosinophils and 1 per cent. Turk cells. The platelets were present in normal numbers and Hess's capillary resistance test was negative. 500,000 units penicillin were given pending the result of the blood count, as the temperature was 100° F. and agranulocytosis was suspected. The face meanwhile had not improved and there were crusted ulcers on the lips. A swab from the mouth ulcers on direct examination showed no monilia or Vincent's organisms; on culture a heavy growth of pneumococci with some coagulase-positive staphylococci was found. No *C. diphtheria* were isolated.

On August 7 the face was flushed and a branny desquamation of the skin on the cheeks was present. There was a crusted weeping eruption on the beard area. Œdema of the neck was noted, the mouth was very painful and swallowing was difficult. The eruption on the abdomen was of a punctate erythematous nature and on the legs the petechial eruption was unchanged. Four-hourly starch poultices on the face were commenced.

On the following day the facial eruption was more severe. The rash on the trunk and legs was fading. A neo-epinine tablet (20 mgm.) was given to be sucked sublingually, but as this produced severe palpitations and tachycardia, it was not repeated.

On August 9 a dermatologist considered that the condition was an acute exfoliative dermatitis due to the antibiotics administered to a patient who had previously shown a seborrhœic tendency. All therapy was stopped and cremor. zinc. oxid. et ol. ric. was applied to the body and legs, and cremor. zinc. with 1 drachm of lotio plumbi. subacet. per ounce, to the face. A sedative drug was prescribed at night in order to relieve the intense irritation which developed with the widespread desquamation of the skin. On August 10 rhonchi were again noted in both lung fields, for which ephedrine was prescribed. On August 12 the rash on the legs had faded in colour and the face was still crusted. Intense pruritus was present, and conjunctivitis was noted. The eyes were treated by irrigation with warm boric acid lotion. Two days later there was slight improvement of the rash on the face and Benadryl 50 mgm. thrice daily as a sedative and antipruritic was prescribed. The temperature, which up to this time had been raised, returned to normal on August 17.

On August 19 an icteric tinge of the conjunctivæ was noted. Liver function tests, urine and stool examinations suggested catarrhal hepatitis. The skin condition and conjunctivitis continued to improve slowly and the jaundice faded, and on September 3 the Icteric Index was below 10. (For results of biochemical determinations see attached table.) On September 9 the skin condition had almost cleared, but the skin was dry to the touch and there was a slight generalised residual superficial branny desquamation.

On October 22 a pneumoperitoneum was induced. On November 15 the E.S.R. was 17 mm. in one hour, and as the skin condition had completely cleared skin sensitivity tests were done. Materials used in this were gauze

squares soaked in 1 per cent. and 10 per cent. streptomycin and P.A.S. in normal saline, and applied to the skin for twenty-four hours. After forty-eight hours there was marked induration and erythema in response to the applications of streptomycin. The P.A.S. provoked no skin reaction, nor did a saline control. On November 22 the areas of skin to which the streptomycin patches had been applied were erythematous, slightly brown in colour, indurated, and superficial desquamation of skin was present. In the areas to which P.A.S. had been applied an itching, faint papular erythema was present. In view of the obvious sensitivity to streptomycin on patch testing and an equivocal response to P.A.S., the patient was given a test dose of 5 G. P.A.S. Forty-five minutes later he complained of a tingling, burning sensation of the skin of the whole body. Eight hours later the face was flushed, the temperature was not raised and there was a scarlatiniform punctate erythema on the abdomen and back. The legs, arms, conjunctivæ and mouth were unaffected. There was no enlargement of the cervical lymph glands. In the area to which the P.A.S. patch test had been applied erythematous papules were present. Throughout the following three days the skin condition did not change in appearance, and on the fourth day slight branny desquamation of the skin over the cheeks commenced. The patient remained afebrile throughout. On the fifth day the rash on the trunk had the appearance of small brown pigmented areas around the cutaneous hair follicles. On the seventh day the rash had completely faded. Ung. aquos was applied to the desquamating area of skin on the face and rehydration of the skin occurred within twenty-four hours.

The attached table shows the results of biochemical estimations done at varying intervals during the patient's illness. It will be noted that there is evidence of hepatic dysfunction three and a half months after the initial acute episode.

Discussion

The cause of the hepatic dysfunction in the above patient is obscure. He had received no previous intravenous injections and there were no other cases of infective hepatitis in the hospital. There was no history of previous allergy. The strongly positive skin patch reaction to streptomycin is very suggestive that streptomycin was the factor responsible for the hepatitis. In view of the mild skin reaction produced by the test dose of 5 G. P.A.S. without alteration in the blood or urine chemistry, and without pyrexia, it seems unlikely that P.A.S. was the cause of the hepatitis. That the hepatitis was allergic (as in Julian's case) is suggested by the eosinophilia and this has been reported in patients developing jaundice while on P.A.S. alone or combined streptomycin and P.A.S. therapy (Steel, 1952; Thomas, 1952; Fergusson *et al.*, 1952; Jeffery *et al.*, 1952; Cuthbert, 1950; McKendrick, 1951).

The toxic effects of streptomycin include vertigo, blurring of vision, auditory nerve lesions, impaired kidney function with albuminuria and cylinduria, agranulocytosis, drug fever and skin lesions. The skin eruptions which may be provoked are urticaria (which is rare), erythematous pruritic rashes lasting five to six days and exfoliative dermatitis. This last condition is an absolute indication for stopping streptomycin (U.S. Veterans Administration, 1948; Cuthbert, 1952). Among the toxic reactions to P.A.S. are drug fever, usually occurring two to four weeks after commencement of treatment, pruritic skin eruptions, renal damage, a raised prothrombin time (Madigan *et al.*,

1950), enlarged lymph nodes and cardiac irregularities due to lowered blood potassium. Nausea, vomiting and diarrhœa and fat intolerance are extremely common in patients undergoing treatment with P.A.S. and are not a manifestation of toxicity (Steel).

Jaundice due to P.A.S. administration is not uncommon and Thomas (1952) has recently reviewed the literature on this subject.

Julian (1952) suspected that the abnormal liver function tests and skin eruption in a patient on streptomycin and P.A.S. were possibly due to meta-amino-phenol impurities in the P.A.S. in view of the eosinophilia, a positive patch test reaction to P.A.S. (20 per cent), and effective desensitisation in his case. Cuthbert (1950) ascribed the liver dysfunction to allergic thickening of tissues or a toxic side effect of P.A.S. Thomas (1952) has indicated that jaundice usually follows morbilliform or scarlatiniform eruptions, the time interval between the onset of the skin eruption and the jaundice varying between two and ten days. Furthermore, the incidence of hepatitis is unrelated to P.A.S. dosage. Steel (1952) states that antihistamine drugs do not prevent P.A.S. allergy, and allergic manifestations may develop during the administration of antihistamine compounds. Jeffery *et al.* (1952) in discussing a case of acquired hypersensitivity to sodium P.A.S. streptomycin and penicillin state that streptomycin in the pure form now available seems to have no deleterious action on the liver either in man or experimental animals. Riggins and Hinshaw (1949), however, cite a case of severe liver pathology presumably due to streptomycin.

Desensitisation to streptomycin and P.A.S. is a practical procedure, but in view of the fact that the systemic reaction to streptomycin and P.A.S. was so marked in the case quoted above, and the presence of a strongly positive patch test to streptomycin, it was felt that desensitisation would have been too hazardous a procedure. It is not possible to state whether the local application of streptomycin to this patient's operative wound acted as a sensitising mechanism to streptomycin. In view of the long delay before the onset of symptoms it is thought unlikely.

Previous authors have mentioned the importance of careful watch on the temperature chart in patients on streptomycin and P.A.S. therapy, and this pyrexia should always be regarded as a manifestation of drug sensitivity unless proved otherwise. Skin reactions without pyrexia may, however, occur. It is felt that as it is impossible to predict which patients receiving chemotherapy are likely to acquire hypersensitivity to the antibiotics in use, attention should be paid not only to the temperature chart, but also to any mild premonitory symptoms complained of by the patient (Corboy, 1952). Furthermore, in spite of the relative infrequency of streptomycin reactions, streptomycin would appear to be a potentially dangerous hepatotoxic agent, and further studies along these lines are necessary.

Summary

A case of acquired hypersensitivity to streptomycin and P.A.S. resulting in exfoliative dermatitis and jaundice is presented. Streptomycin as a possible cause of the jaundice and the role of P.A.S. in the production of jaundice is discussed.

TABLE I.—BIOCHEMICAL DETERMINATIONS

Date	*Liver Function Tests*	*Blood Count*	*Urine*	*Serum Bilirubin or Icteric Index (I.I.)*	*Fæces*
26.6.52			Nil abnormal		
30.6.52	Thymol turbidity (T.T.) 3 U $ZnSO_4$ turbidity = 8 U Scarlet red flocculation (S.R.) = 0 Cephalin-cholesterol flocculation (C.C.) = +		Urobilinogen not increased		
1.7.52		Hb = 12·8 G. % W.B.C. 9,200 (P. 71·5% (L. 26·0% (M. 1·5% (E. 1·0%			
8.8.52		Hb = 15·6 G. % W.B.C. 27,000 (P. 49·5% (L. 16·0% (M. 2·5% (E. 31·0% Platelets 300,000	Nil abnormal		
11.8.52			Nil abnormal		
12.8.52			Nil abnormal		
19.8.52			Bilirubin + Urobilinogen – slight increase Protein nil	v.d. B. direct + v.d. B. indirect 1·75 mgm. % I.I. 20	Stercobilin +
21.8.52	T.T. 18 U $ZnSO_4$ T. = 20 U C.C. + + + Serum albumin 2·7% Serum globulin 3·5%			I.I. 14	
3.9.52	T.T. 16 U $ZnSO_4$ T. = 20 U C.C. + + + S.R. + + +			I.I. below 10 Serum bilirubin nil	
4.9.52			Urobilinogen not increased		

Date	*Liver Function Tests*	*Blood Count*	*Urine*	*Serum Bilirubin or Icteric Index (I.I.)*	*Fæces*
9.9.52			Urobilinogen not increased		
11.9.52		Hb = 12·8 G. % W.B.C. 8,600 (P. 63·5% (L. 29·0% (M. 1·5% (E. 6·0%			
16.9.52	T.T. 14 U $ZnSO_4$ T. = 16 U C.C. + + S.R. + + +			I.I. 3	
29.10.52	T.T. 7 U $ZnSO_4$ T. = 11 U C.C. + + S.R. + + +		Bilirubin nil	I.I. 4 Serum bilirubin 0·2 mgm. %	
24.11.52	T.T. 7 U $ZnSO_4$ T. = 10 U C.C. + + S.R. + + + Formol gel test = negative Serum albumin 3·6% Serum globulin 3·6%	Hb = 13·9 G. % W.B.C. 6,800 (P. 61·5% (L. 28·5% (M. 9·0% (E. 1·0%	Bilirubin nil Urobilinogen nil	I.I. 5 Serum bilirubin 0·2 mgm. %	

REFERENCES

BIGNALL, J. R. (1952): *Tuberc. Index*, **7**, 219.

CORBOY, A. F. (1952): Personal Communication.

CUTHBERT, J. (1950): *Lancet*, **2**, 209.

CUTHBERT, R. J. (1952): *Brit. Med. J.*, **2**, 1205.

FERGUSSON, A. G., MCINTYRE, J. P., and GEMMELL, A. R. (1952): *Brit. Med. J.*, **1**, 855.

JEFFERY, B., BORRIE, P., and MACDONALD, N. (1952): *Brit. Med. J.*, **2**, 647.

JULIAN, D. G. (1952): *Brit. Med. J.*, **2**, 476.

MADIGAN, A. G., GRIFFITHS, L. L., LYNCH, M. J. G., BRUCE, R. A., KAY, S., and BROWNLEE, G. (1950): *Lancet*, **1**, 239.

MCKENDRICK, G. D. W. (1951): *Lancet*, **2**, 668.

RIGGINS, H. M., and HINSHAW, H. C. (1949): "Streptomycin and Dihydrostreptomycin in Tuberculosis," Nat. Tuberc. Ass.

STEEL, S. J. (1952): *Brit. Med. J.*, **1**, 415.

THOMAS, J. H. (1952): *Tubercle*, **33**, 329.

U.S. VETERANS ADMINISTRATION, St. Paul, Minn.: Minutes of 6th Streptomycin Conference. Reported in *Tuberc. Index* (1950), **5**, 439.

ADENOCHONDROMA OF LUNG

A REPORT OF FIVE CASES

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Benign tumours of lung consisting chiefly of cartilage are uncommon. They have been called chondroma of lung, chondroma of bronchus, mixed tumour and hamartoma. For reasons discussed below we think a more correctly descriptive term is "adenochondroma of lung" as suggested by C. B. McGlumphy (1924). Until recently many of the examples recorded had been found incidentally during a port-mortem examination, but with the widespread use of X-ray examination of the chest a greater number are now being discovered during life, when they generally present something of a diagnostic problem.

We here present a short account of five cases, three found during life and two discovered at autopsy.

Case 1

A man aged 65 was admitted to hospital in May 1951 with a history of loss of weight for one year and dysphagia for five weeks. Investigations showed an almost complete neoplastic obstruction at the lower end of the œsophagus. For the past seven years he had suffered from asthmatic attacks and a productive cough, worse in winter. Previously he had had no respiratory symptoms. There were physical signs and radiological evidence suggestive of bronchiectasis in the lower lobe of his right lung. Routine examination also revealed a fairly advanced, but symptomless, carcinoma of the rectum.

In view of his severe dysphagia a left thoracolaparotomy was performed and an advanced carcinoma at the cardiac end of the stomach was resected with the performance of an œsophago-gastrostomy.

His condition rapidly deteriorated after operation and he died on the second post-operative day.

The removed carcinoma of the stomach was a well-differentiated adenocarcinoma.

Post-mortem examination showed a well-differentiated mucus-secreting adenocarcinoma of the rectum, histologically different from the carcinoma of the stomach.

In the lower lobe of the right lung there was a polypoid tumour, 2 by 0·7 cm., arising in and blocking the posterior basic segment bronchus (Fig. 1). The bronchi distal to it showed gross bronchiectasis.

Histological examination of this tumour showed it to consist mainly of adipose tissue with only one or two small islands of cartilage. There were also several fine curving bands of bone enclosing normal active bone marrow (Fig. 2). The surface projecting into the bronchus was covered by a single layer of flattened epithelium.

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Fig. 1.—Half the circumference of the right lower lobe

FIG. 1.—Half the circumference of the right lower lobe bronchus cut transversely, showing the tumour projecting into the lumen with the typical lobulated surface.

FIG. 2.—Section of tumour from Case 1 showing cartilage, adipose tissue and a thin, curving band of bone surrounding an island of bone marrow.

FIG. 3.—Radiograph of chest from Case 2, showing small round opacity in right lung.

FIGS. 4 and 5.—P-A and lateral radiographs from Case 3, showing large opacity in region of right middle lobe.

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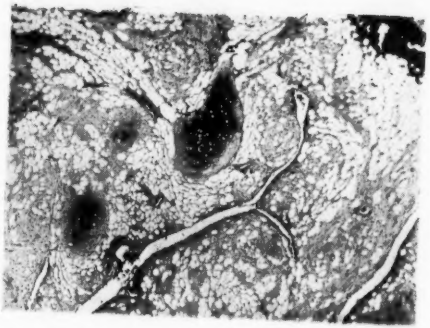
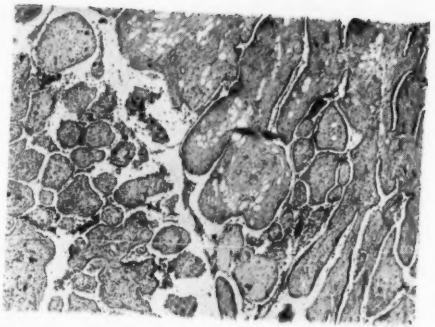
FIG. 6.—Cut surface of tumour from Case 3 surrounded by compressed lung tissue. (Magnification $\times 1\frac{1}{4}$.)





FIGS. 7A and B.—Sections from tumour of Case 3 showing the mixed nature of the connective tissue element. (A) shows an island of cartilage and much adipose tissue; (B) is from a papillary area.

FIG. 8.—Cut surface of right upper lobe and left lung (Case 4) showing tumour. (Magnification $\times 1\frac{1}{4}$.)

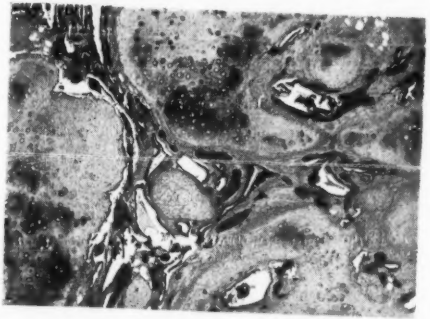


FIG. 9.—Section of tumour of Case 4 showing large islands of cartilage with intervening narrow clefts lined by epithelium.

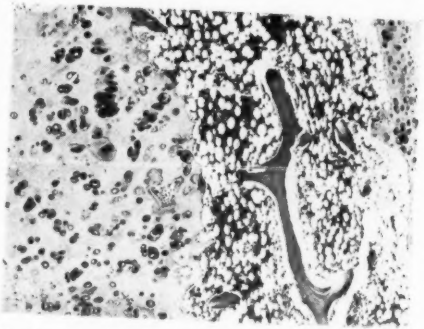


FIG. 10.—Cricoid cartilage from a man of 63 showing typical endochondral ossification.

CASE 2

The second patient was a man aged 30. In May 1948 he had a vagotomy performed through a left transthoracic approach for a duodenal ulcer and no abnormality had been reported on radiological examination of his lungs at that time.

He was readmitted in June 1952 with a recurrence of his dyspepsia, and a routine chest X-ray showed a small round opacity in the right lung (Fig. 3). He had had no respiratory symptoms.

Although it was felt that the tumour in the lung was probably simple (*e.g.*, an adenoma), the fact that it might be an early peripheral carcinoma of the lung or a single metastasis could not be ruled out. Full X-ray examination of his other systems showed no abnormality apart from a duodenal ulcer.

The right lung was therefore explored through a thoracotomy incision and a small, hard, round tumour was felt just beneath the pleura on the lateral surface of the pectoral segment of the right upper lobe. The lung tissue over it was incised and the tumour, which was about 1·5 cm. diameter, shelled out very easily. It had a lobulated surface, was whitish-grey on the cut surface, and quite firm in consistency. It appeared to have no bronchial connection. The patient's post-operative course was satisfactory.

Histological examination showed the tumour to consist of large masses of rather cellular cartilage. These masses of cartilage merged gradually into narrow fibrous trabeculæ which divided the masses from one another. This fibrous tissue was rather cellular and mucoid. It included in one area a small amount of adipose tissue and some smooth muscle. The periphery of the tumour was covered by a single layer of flattened epithelium that at some points appeared more cubical. In one area were a few small clefts lined by low columnar epithelium.

CASE 3

This patient, a woman aged 53, was admitted to hospital in September 1952. One year previously she had been X-rayed by a Mass Radiography Unit at her place of employment and a shadow had been seen in the right lung. At that time she had no symptoms and refused to go to hospital for further advice. During the next few months she began to get tired easily, but developed no other symptoms. Six years previously two of the patient's daughters had been treated for pulmonary tuberculosis and had responded after a period of bed rest. The patient herself had not been X-rayed at that time.

X-rays (Fig. 4) at the time of admission showed a large round, discrete tumour in the anterior part of the right lung, and one view showed sufficient definition of the right middle lobe bronchus to localise the tumour in that lobe. Bronchoscopy was negative, the right middle lobe bronchus appearing normal. Pre-operative diagnosis lay between adenoma, peripheral carcinoma or tuberculoma.

A thoracotomy was performed and a round, hard tumour about 4 cm. diameter was felt in the right middle lobe. It was well clear of the hilum and a dissection lobectomy was performed without any difficulty.

When the lobe was cut after operation the tumour was firm in consistency, whitish-grey on the cut surface, lobulated, and easily shelled out of the lung substance. It had no connection with any visible bronchus (Fig. 5).

The immediate post-operative course was satisfactory, but on the ninth post-operative day she developed auricular fibrillation and three days later

FIG. 16.—Cricoid cartilage from a man of 63 showing typical endochondral ossification.

FIG. 3.—Section of tumour of Case 4 showing large islands of cartilage with intervening narrow strands lined by epithelium.

(Case 4) showing tumour. (Magnification × 14.)

had a cerebral embolism with a left hemiplegia. This has shown but gradual recovery.

Histological examination showed the connective-tissue component of the tumour to be very mixed. It contained a large amount of adipose tissue, circular masses of cartilage, and areas of cellular fibrous tissue.

In addition to the broad masses of tumour covered with low columnar or cubical epithelium, there were quite large areas of a much finer papillary structure with fronds of tumour having a rather cellular fibrous tissue core and an epithelial covering (Fig. 6).

Case 4

A man aged 55 years was admitted to hospital in November 1949 with a lesser curve gastric ulcer of eleven years' duration. He had no symptoms referable to his respiratory tract. X-ray of his chest was reported normal apart from some emphysema. There were two small calcified opacities in the hilum of his left lung, but these were presumed to be calcified glands. Following a partial gastrectomy for the peptic ulcer, he developed paralytic ileus with peritonitis and died on the seventh post-operative day. Post-mortem examination showed ileus with an extensive fibrino-purulent peritonitis.

In the posterior part of the upper lobe of the left lung was a firm nodular mass 1 cm. in diameter (Fig. 7).

Histological examination showed the tumour to be made up mainly of large oval or circular areas of cartilage. Some were separate, but some were joined to one another to form complex branching masses. Between these were narrow bands of fibrous tissue and, especially at the periphery of the tumour, they contained numerous branching clefts lined by low columnar epithelium. These clefts were so numerous in places as to suggest participation by the epithelium in the tumour process (Fig. 8).

Case 5

A man of 59 died soon after admission to hospital, having been diagnosed as suffering from a cerebral hæmorrhage. Post-mortem examination showed evidence of long-standing hypertension and a large intracerebral hæmorrhage destroying the basal ganglia of the right cerebral hemisphere. In the posterior part of the lower lobe of the right lung was an irregular round tumour 1·7 cm. in diameter, of tough cartilaginous consistency and not obviously connected with a bronchus.

Histological examination showed a tumour consisting of large oval and circular masses of cartilage that were closely packed together. Their surfaces were covered by a single layer of low columnar epithelium. The close approximation of these surfaces resulted in the formation of narrow epithelial lined clefts between the cartilaginous nodules.

Discussion

There appears to be a certain amount of confusion regarding the nature and designation of these tumours. Hochberg and Pernikoff (1950) make a distinction between the chondroma of lung and the hamartoma, although it is not at all clear on what they base this distinction. They include, however, in their series of collected cases of so-called chondroma those described

by Goldsworthy (1934) and Willis (1948), tumours that are clearly the same as those described here.

Although these tumours vary in the relative amounts of epithelium and connective tissue present, and also in the type of connective tissue, there is no doubt that they represent variations of the same tumour. Those with the smallest amount of epithelium (Cases 2 and 5) consist almost entirely of cartilage. In Case 3 the connective-tissue component was very mixed and parts of the tumour showing no cartilage were papillary with fibrous tissue stroma.

The tumour in Case 1 is of interest because, in addition to adipose tissue and well-formed bony trabeculæ, it contained hæmopoietic bone marrow. The appearances in fact closely resemble the ossification seen in the laryngeal cartilages in old age (Fig. 9), and it seems likely that this tumour may have contained a good deal of cartilage which has undergone this very common process of endochondral ossification. Adipose tissue does occur apart from this process, as in Case 3 (Fig. 6). Occasionally it may form a large part of the connective tissue of the tumour, and lipomas of the bronchus should be fully investigated to ensure that they are not examples of these tumours with predominantly adipose connective tissue.

In all the tumours there is an epithelial as well as a connective-tissue component. In view of this it is felt that the name "adenochondroma" is a suitable one. Any attempt to recognise in the name the variable components of the connective-tissue part of the tumour would lead to undue complication. It appears that, rarely, basically similar lesions may occur with no cartilage in the stroma. The two cases of fibro-adenoma described by Scarff and Gowars (1944) closely resemble parts of the tumour in Case 3.

It has been suggested at various times that these tumours are not true neoplasms but are what Albrecht (1904) described as hamartomata—that is, tumour-like malformations in which there is abnormal mixing of the normal tissues of the organ. The abnormality may affect the amount, arrangement or degree of differentiation and is assumed to arise by abnormal mixing or from disturbance of their development. The classical example of this is the common cutaneous angioma. Such lesions grow only as the body grows. Moreover, they are almost invariably present at birth, as the disturbance resulting in their formation occurs during development. Albrecht also suggested that occasionally hamartomata develop in adult fully differentiated tissues. It is difficult to see any distinction between such lesions arising during adult life and true neoplasms. It seems more logical to confine the term "hamartoma" to lesions arising during development and growing only as the body grows (Willis, 1948).

Accepting this definition, there is evidence in three of our cases against the view that the lesions are hamartomata and in favour of regarding them as true tumours.

In Case 1 there is a definite history of the development of symptoms suggestive of bronchiectasis seven years before death. This, combined with the finding of bronchiectasis at autopsy, is strong evidence of the growth of the tumour during this time. In Case 2 the chest was X-rayed and the patient was screened on several occasions in 1948, and if the lesion found in

1952 had been present then it would certainly have been seen. Finally, in Case 3 there is a suggestion of an increase in size of the tumour in the year between the two radiographs of her chest.

Hochberg and Pernikoff (1950) collected 75 cases from the literature and added 3 cases of their own. Of the cases in which the information was available, 50 were males and 13 females, 38 were in the right lung and 24 in the left. Including our cases, the total number now recorded is 83, 54 males and 14 females, 42 right-sided and 25 left-sided.

The symptoms arising from adenochondromas depend on their size and position. The peripheral type of growth usually causes symptoms only by virtue of its size. Occasionally they may cause erosion of a small vessel with hæmoptysis. Since many of these tumours are small they are usually discovered only on routine radiological examination of the chest or at autopsy. The tumours arising in relation to the wall of a bronchus may cause cough by irritation, but most of their effects are due eventually to some degree of bronchial obstruction. They then may be mistaken for more common tumours, such as carcinoma or adenoma, or they may simulate bronchiectasis or even tuberculosis.

Radiological examination of the chest may reveal a fairly dense, well-defined, round or oval tumour in the lung substance. In cases of bronchial obstruction the X-ray evidence will be that of collapse or of obstructive pneumonitis. The intrabronchial type may be seen on bronchoscopy and will be firm in consistency and may be covered with normal mucous membrane.

Treatment will depend on the site of the tumour. When bronchial obstruction is present, perhaps with well-defined secondary bronchiectasis or pneumonitis, lobectomy or segmental resection is indicated. When the tumour is present in a large bronchus, without disorganisation of the lung beyond, it could conceivably be removed locally by bronchotomy, as is occasionally possible in adenoma of the bronchus (d'Abreu and McHale, 1952). The peripherally located tumours will often be thought to be peripheral primary carcinoma of the bronchus, adenoma, a single secondary carcinoma, or a tuberculoma. Since this type of chondroma can easily be shelled out from the lung substance it is worth incising down on to any doubtful tumour before proceeding to resection. In the second case reported here this procedure was carried out with success. In the third case the tumour could easily have been shelled out of the right middle lobe had this procedure been attempted.

Summary

(1) Five cases of chondroma or adenochondroma of the lungs are reported.

(2) The histology of these cases and of others from the literature is discussed and it is suggested that the term "adenochondroma of the lung" is a more suitable description of the condition than the other terms commonly used.

(3) Some suggestions regarding diagnosis and treatment are made.

We wish to express our thanks to Mr. A. L. d'Abreu and to Professor J. W. Orr for their permission to use the clinical and pathological material respectively and also for their helpful advice in the preparation of this article.

REFERENCES

ALBRECHT, M. (1904): *Verh. Dtsch. Path. Ges.*, **7**, 153.
D'ABREU, A. L., and MCHALE, S. J. (1952): *Brit. J. Surg.*, **156**, 355.
GOLDSWORTHY, N. E. (1934): *J. Path. Bact.*, **39**, 291.
HOCHBERG, L. A., and PERNIKOFF (1950): *Dis. Chest.*, **17**, 337.
MCGLUMPHY, C. B. (1924): *J. Cancer Research*, **8**, 482.
SCARFF, R. W., and GOWARS, F. J. S. (1944): *J. Path. Bact.*, **56**, 257.
WILLIS, R. A. (1948): "Pathology of Tumours," pp. 7 and 383, Butterworth's Medical Publications.

SARCOIDOSIS PROCEEDING TO OPEN PULMONARY TUBERCULOSIS, WITH SUBSEQUENT RECOVERY

(WITH REPORT OF A CASE)

By G. P. Maher-Loughnan,
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This case history is of interest because it traces in a Coloured man the natural evolution from Boeck's sarcoidosis to acute tuberculous lobar pneumonia. Subsequent events, leading back radiographically and immunologically to a phase similar to the pre-tuberculous and to the pre-sarcoid stage, are also noteworthy.

Case Report

H. E. B., aged 40, a native of the Gold Coast, had served as ground-crew with the R.A.F. during the war. Routine examination in 1945 revealed splenomegaly, attributed to childhood malaria.

In 1946 a routine film was taken and "increased lung markings" were reported. From that time he reported sick at intervals, but was told that he had "a touch of bronchitis" until early in 1949, by which time his cough was severe and associated with marked dyspnœa.

A radiograph revealed fine mottling throughout both lung fields, more dense in the middle and lower zones (Fig. 1). The sputum was repeatedly cultured but no *M. tub.* were grown. Mantoux tests were negative to strengths of 1/100; no eye or bone lesions were discovered. An axillary gland was removed and a section sent to Dr. Robb-Smith at Oxford, who considered that the specimen confirmed the tentative diagnosis of sarcoidosis. In October 1949 the man was discharged from the R.A.F. His symptoms were unaltered, his weight was steady, sputum was persistently negative on culture to *M. tub.*, and the skin remained insensitive to 1/100 O.T.

The patient remained at home under Chest Clinic supervision for ten months. In August 1950 the cough became very troublesome and productive of copious mucopurulent sputum. Radiographs (Fig. 2) revealed consolidation of the right upper zone with gross excavation. There was some infiltration in the apex of the right lower lobe and, for the first time, the sputum was found to contain *M. tub.* in large numbers.

He was admitted to hospital, and in view of the recent bacteriological findings the biopsy specimen, mounted in 1949, was re-examined by Professor Dible at the Post-Graduate Medical School. He reported that although the slide was technically imperfect, "it is reasonably certain the lesion present is sarcoidosis. It consists of small, discrete, epithelioid tubercles without caseation but with frequent concentric hyalinisation. No inclusion bodies seen." A course of 48 gm. streptomycin with P.A.S. was given with little significant change, and in October 1950 a pneumoperitoneum and a right phrenic crush were performed.

In November 1950 he was transferred to Colindale Hospital, a very sick man. He was emaciated—having recently lost 2 stone in weight—markedly orthopnœic, with a severe and intractable cough producing 2 oz. of muco-

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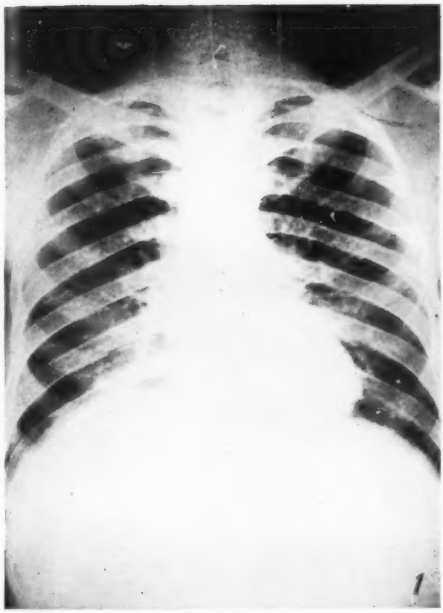

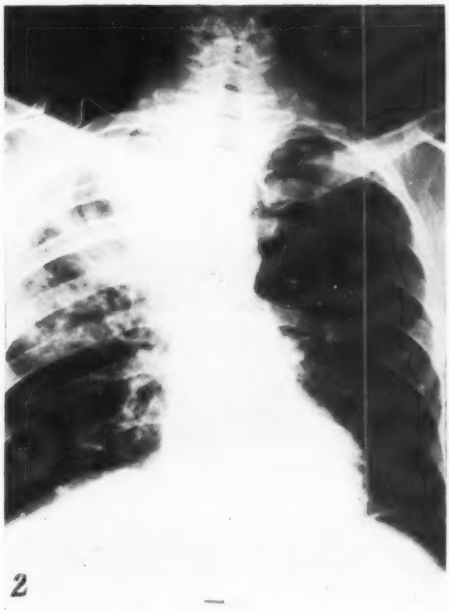

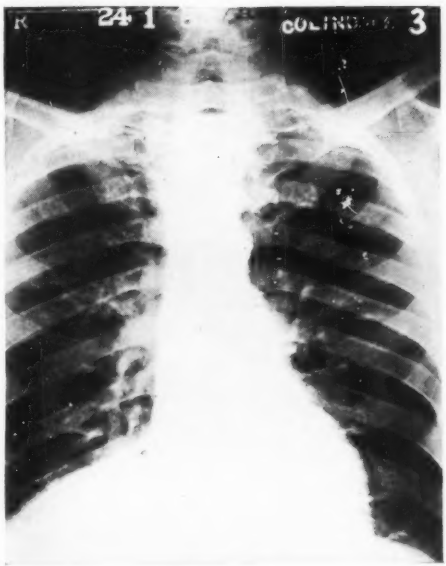

FIG. 1.—Film taken on 3.10.49. Showing fine reticulation and hilar adenopathy of sarcoidosis.

FIG. 2.—Film taken on 23.8.50. Demonstrating superimposed acute tuberculous involvement in the right lung.

FIG. 3.—Film taken on 24.1.53. Lung fields now relatively normal.

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purulent sputum daily which contained tubercle bacilli. Abnormal physical signs were confined to the upper half of the right hemithorax and were suggestive of consolidation. A radiograph revealed, however, that, with elevation of the right side of the diaphragm, atelectasis had become superimposed on pre-existing consolidation, with the appearance of gross cavitation.

After a preliminary period of observation, during which time the cough and dyspnœa persisted to a distressing extent, it became apparent that the first aim was to allow the diaphragm to descend as far as possible and to start another course of chemotherapy.

Accordingly the air in the P.P. was allowed to reabsorb and only very small refills were continued. After a further 56 gm. of streptomycin and P.A.S. there was a distinct relief of symptoms and some radiological improvement. Consolidation persisted in the right upper lobe as did the fine reticulation and hilar adenopathy originally attributed to the sarcoidosis, but cavitation could no longer be demonstrated and the massive collapse was no longer evident. The sputum became negative on direct examination; positive cultures were grown for the last time at this phase.

P.A.S. was continued alone for another two months. Then, on reviewing the case, it was apparent that, although initial clinical and radiological improvement had been maintained, the extent and degree of consolidation in the right upper lobe was unchanged. Accordingly, after ascertaining that a brisk skin reaction followed intradermal injection of 1/10,000 dilution of O.T., a course of tuberculin injections was started. Primarily 0·1 c.c. of 1/10,000 O.T. was given by i.m.i., and increasing strengths were given at regular intervals until, three months later, 1 c.c. of pure tuberculin was given and this dose was repeated weekly for one month. The Mantoux reaction lessened progressively until finally there was no response to 1/10 dilution. Concurrently another course of chemotherapy was given, this time with intermittent doses of 2 gm. streptomycin every third day, for 4 months, 64 gm. being given, bringing the total of streptomycin to 166 gm.

During this phase there was progressive clearing of the consolidation, until by August 24, 1951, at the end of the course, only a small area of consolidation remained at the extreme apex of the right lung, the hilar shadows had become less marked, and there was a generalised reduction of reticulation in the remaining lung fields.

During the next three months the patient's general condition continued to improve. The cough steadily improved, the sputum diminished and remained negative on culture, the B.S.R. fell steadily from 60 mm. to 6 mm. per hour.

The P.P., which had been maintained minimally, was finally abandoned early in October 1951 and the patient started to get up. At the end of November 1951 he was discharged home. He was then walking three miles daily, he had steadily regained 2 stone in weight and his general condition had greatly improved, radiographic improvement continued, there were then no residual areas of consolidation and tomograms showed no evidence of cavitation. Mantoux tests were repeated and the skin still showed no response to 1/100 strength O.T.

On January 24, 1953, the patient was seen again: his general condition was excellent; he had returned to full-time work and felt perfectly well. An X-ray was taken and is reproduced here (Fig. 3); the generalised mottling has now largely cleared, and there is only a small scarred area apparent in the right upper lobe. The Mantoux test was mildly positive to 1/100 dilution O.T. He had still a trace of sputum which remains culture negative, a slight cough

persists, but the dyspnœa has progressively improved. The weight has been maintained and the B.S.R. was 2 mm. per hour (Westergren).

Discussion

Since pulmonary sarcoidosis was first described it has been recognised that no clear-cut line can be drawn between this condition and chronic miliary tuberculosis. Ustvedt re-emphasised the point when, in 1948, he described a case which, diagnosed as sarcoidosis, was found at autopsy one year later to have typical chronic miliary tuberculosis; he admitted, however, that it is not certain that this condition was additional to a pre-existing sarcoidosis. Scadding (1950) described the distinction between the conditions as being frequently little more than a verbal one. He considered, however, that when open tuberculosis supervenes in this type of case the prognosis is gravely affected. Ruben and Pinner (1944) recorded how rarely open tuberculosis occurred in association with sarcoidosis; and Salvesen (1936) described an unusual case where sarcoidosis developed on pre-existing tuberculous calcified lesions.

Reisner (1944) emphasised the preponderance of coloured subjects contracting sarcoidosis, in a ratio of 6/1 over whites. He described how, when pulmonary tuberculosis developed, an acute exudative or pneumonic process was manifest, and all these cases died. He emphasised the static appearance in sarcoid lesions over a period of years and the occasional tendency to spontaneous regression and apparent resolution, which suggests that at some phase of the disease the pathological changes may be reversible.

In the present case the course of the disease was very similar to that outlined by Reisner. Some three years after radiological changes were first noted, pulmonary sarcoidosis was diagnosed on biopsy, X-ray appearances and absence of skin reactions. A further eighteen months passed before a change occurred, clinically manifest by an increase in cough, sputum and general malaise, and radiographically by a superadded lobar pneumonic condition with gross cavitation which subsequently proved to be tuberculous in nature (Fig. 2).

The treatment both of sarcoidosis and of breaking-down miliary tuberculosis is still undetermined. A point conceded by Moyer and Ackermann (1950), by Pulaski and White (1948) and by Scadding (1950) was that tuberculin and streptomycin singly had each proved ineffective. Scadding described how some improvement had resulted, in one case dramatically, with the use of calciferol for five months.

In the case here described streptomycin and P.A.S. had produced some improvement but the position had remained static for some months. Pneumoperitoneum and a phrenic crush had not contributed to the improvement; in fact, while the superadded massive collapse lasted, his condition deteriorated rapidly.

Having determined, as a matter of interest, the brisk skin response to 1/10,000 tuberculin in a subject who was previously and repeatedly insensitive to 1/100 dilution, a theoretical approach to the therapeutic problem was evolved. It was thought that, by a desensitisation process, it might be possible to lessen the degree of œdema in the affected parenchymal and bronchial

tissues. Streptomycin was given also so that, should the tissue fluid content thus be diminished by the desensitisation, greater concentrations of the antibiotic would reach the infected areas.

Desensitisation was carried out fully, so that finally no skin response occurred even to 1/10 tuberculin. The radioscopic improvement, which was so dramatic, occurred not concurrently but some 8 to 10 weeks after the course was concluded.

This case has been recorded simply for its interest value. It may act as a straw in the wind, pointing to an effective therapeutic approach to the rare yet grave progress from sarcoidosis to open pulmonary tuberculoisis; on the other hand, the spontaneous resolution of lesions may have been coincidental to treatment, owing to a change in the patient's own resistance.

There are three logical therapeutic channels to be explored before accepting the hypothesis of coincidence.

(1) Repetition of the régime of treatment when and if another such case appears. So rare is the combination that some reader, having such a subject as a patient, might wish to repeat the course; this would help to confirm or refute its therapeutic efficiency.

(2) Sometimes areas of tuberculous consolidation will not respond satisfactorily to chemotherapy. It is intended to study a few of these cases to explore the degree of sensitivity to tuberculo-protein, and to endeavour to alter the sluggish response to treatment by altering the allergic state.

(3) As a corollary to the present approach, and as a parallel to the pathological changes in this case, it is hoped to study a few cases of progressive or static sarcoidosis, to attempt to sensitise the anergic subjects (up to a brisk response to 1/10,000 tuberculin) giving streptomycin concurrently as a safety measure, and to study the resulting effect on the lesions.

Summary

A case is presented demonstrating a remarkable degree of regression of long-standing pulmonary sarcoidosis, with healing of more recent open tuberculous disease. The natural development of the disease in this case is outlined, and it is suggested that the therapeutic method of desensitisation to tuberculo-protein under cover of streptomycin and P.A.S. may have favourably affected the grave prognosis of this disease complex.

I wish to thank Wing Commander R. M. Cross, commanding the R.A.F. Institute of Pathology and Tropical Medicine, Halton, for his report and for the biopsy specimens relating to this man. I am also indebted to Professor J. Henry Dible, the British Post-Graduate Medical School, for permission to publish his earlier pathological report.

REFERENCES

MOYER, J. H., and ACKERMANN, A. J. (1950): *Amer. Rev. Tuberc.*, **3**, 299.
PULASKI, E. J., and WHITE, T. T. (1948): *Archives Inter. Med.*, **82**, 217.
REISNER, D. (1944): *Amer. Rev. Tuberc.*, **49**, 289 and 437.
RUBEN, E. H., and PINNER, M. (1944): *Amer. Rev. Tuberc.*, **49**, 146.
SALVESEN, H. A. (1936): *Acta. Scanda. Meda*, **86**, 127.
SCADDING, J. G. (1950): *Brit. Med. J.*, **1**, 745.
USTVEDT, H. J. (1948): *Tubercle*, **29**, 107.

THE DEVELOPMENT OF ARTERIOVENOUS ANEURYSMS IN THE LUNG

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Congenital arteriovenous aneurysms arise from the persistence of an embryonic vascular arrangement in the fully developed organ. These lesions, although congenital, frequently develop during adult life; they are usually multiple and may be present in more than one member of a family. They show some diversity of structure, but always have, as a basic feature, a precapillary communication between an artery and a vein which lacks the specific neuromuscular control of the physiological Sucquet-Hoyer canals.

The first case of arteriovenous aneurysm in the lung was recorded by Wilkens (1917) as "multiple pulmonary aneurysms." A woman of 23 years who had died following a massive hæmothorax had presented all the "classical" features of the disease. At the age of 16 she began to have attacks of epistaxis. This was followed by increasing cyanosis, progressive dyspnœa, a dry cough and the appearance of telangiectatic spots on the lips and tongue. The heart was enlarged and over an area of dullness in the left lung a systolic bruit was heard. Finally a precordial thrill and an apical systolic murmur appeared, accompanied by swelling of the ankles. The autopsy revealed "multiple aneurysms" with free communications between arteries and veins. The only cardiac anomaly was a patent foramen ovale.

Similar cases were recorded by Reading (1932) as "congenital telangiectasis in the lung," by Bowers (1936) as "hæmangiomata" and by Rodes (1938) as "multiple angiomata," before Smith and Horton (1939) made the first clinical diagnosis of "arteriovenous fistula in the lung." These later papers have shown that polycythæmia accompanies the cyanosis and that hæmoptysis, numbness, tingling and epileptiform attacks may be additional symptoms; while cardiac enlargement, epistaxis and superficial telangiectasis are not always present.

More important additions to our knowledge were made by Hepburn and Dauphinee (1942), who recorded Shenstone's successful treatment of a case by pneumonectomy, and by Whitaker (1946), who demonstrated that the diagnosis could be made on the radiological appearances alone in the case of a patient free from all symptoms and other signs.

Although over 100 cases have been reported in the literature under a variety of names, only once has the true nature of the lesion been demonstrated by dissection (Hayward and Reid, 1949). These writers state that "doubt about the pathology is responsible for the confusion in the naming of the condition," and they demonstrate how mistaken impressions may be obtained by study of the section alone. Another method of demonstrating the structure is by making a cast of the lesion and then dissolving away the

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surrounding tissue. This method has been used by Goldman (1948) and Lindskog *et al.* (1950). A third method of studying the morphology is to watch the development of the lesion by means of serial X-rays, and this is the method used by the present writer.

Case Report

In January 1947, a girl aged 17 years had a routine skiagram of her chest which disclosed an opacity in the lower zone of the right lung. (Fig. 1.) At that time no abnormal signs or symptoms were detected and she was kept under observation by a chest clinic for the next sixteen months. During this time the opacity increased in size and the following investigations were carried out: the B.S.R. was 5 mm. in 1 hour, three gastric lavage specimens were negative for tubercle bacilli, there were 6,000,000 red cells with 18 G. of hæmoglobin per 100 c.c.

In May 1948 she was admitted to hospital as a probable case of pulmonary tuberculosis, as not only had the opacity in the right lung increased in size but several small opacities had appeared in the left upper zone. (Fig. 2.)

On examination a slightly built, normally developed girl showed a mild degree of cyanosis of the lips and the nail-beds. There was no evidence of telangiectasia of the skin or mucous membranes, but slight clubbing of both fingers and toes was present. The B.P. was 135/80 and the pulse rate was 80 per minute. No abnormality was detected in the lungs, but a heaving impulse was felt over the præcordium and in the mitral area a harsh systolic murmur was heard. No other abnormalities were found.

There was no previous history of any serious illness, but her family history revealed that her paternal grandmother had had two attacks of hæmoptysis and was slightly cyanosed. Unfortunately the family did not wish to be further investigated.

During the patient's stay in hospital it was noted that the degree of cyanosis varied, being more marked in a warm atmosphere, and that a systolic bruit could sometimes be heard at the base of the right lung, but it was not noted whether the intensity of these signs was related to the menstrual cycle. On further examinations of the cardiovascular system a presystolic but no other diastolic apical murmur was heard, the systolic blood pressure was always slightly above average and the pulse rate never dropped below 80 per minute. On screening the opacity in the right lung it was seen to pulsate, but Muller and Valsalva's manœuvres produced no change in its size. The circulation time was studied with intravenous ether and magnesium sulphate and recorded at 8 seconds and 10 seconds respectively. Although these results were considered to be significant further tests were not carried out, as Taussig (1947) has recorded a death from ether embolism in a case of an intracardiac septal deficiency.

Other investigations were as follows: Tuberculin jelly test and Mantoux 1/1,000 were negative, the B.S.R. 4 mm. in 1 hour, R.B.C. 6,000,000, Hb 18 G. per 100 c.c., W.B.C. 10,000, polymorphs 63 per cent., lymphocytes 37 per cent., Arneth count essentially normal, urinalysis normal, three gastric lavage specimens were negative for tubercle bacilli on culture.

The following diagnoses were considered: pulmonary tuberculosis with a congenital heart lesion, pulmonary tuberculosis with mitral stenosis, and arteriovenous aneurysm with secondary cardiac strain. The first two possibilities were rejected because of the absence of any evidence of pulmonary tuberculosis and the fact that no abnormal cardiac finding was noted during the

preceding sixteen months, a period during which she had had repeated examinations by several doctors. The absence of a rheumatic history also weighed against mitral stenosis and the most probable diagnosis appeared to be arteriovenous aneurysm with secondary cardiac strain. Her parents were advised to have her investigated by a cardiologist, but before this could be arranged the patient took her own discharge.

Subsequently she developed a dry cough and became dyspnœic on exertion. In September 1948 she was admitted to the Brompton Hospital under the care of Mr. Brock, but died before any treatment could be attempted.

A post-mortem performed by Dr. Keith Simpson revealed that death was due to a fresh embolism blocking completely the middle cerebral artery. There was no developmental anomaly of the heart but a well-established rheumatic affection of the mitral valve with stenosis, auricular thrombosis and early affection of the aortic cusps. The lungs were extensively affected by developmental angiomatosis, a particularly large vascular tumour being present in the right lower lobe which bulged from its surface. Elsewhere on its surface there were numerous coursing vessels and occasional fresh intrapulmonary hæmorrhages. No vascular lesion or disease was found in any other organ.

Discussion

Etiology.—The first study of non-traumatic arteriovenous anastomosis was made by John Bell (1801), and as his work is not mentioned in the monographs of Holman (1937) and Leriche (1949), some of his more important observations are recorded here. He defines "the aneurysm from anastomosis" as a tumour consisting of "a congeries of small and active arteries, absorbing veins and intermediate cells," and later states "such is the influence of the anastomosis or communication of vessels in generating, supporting, feeding and augmenting this tumour that I know of no name so proper as aneurysm by anastomosis." On the etiology he writes, "it arises from various and hidden causes," and lists as adjuvant factors trauma, menstruation, exercise, heat and alcohol. Later writers have been able to add little to our knowledge of the hidden causes, for while Clark and Clark (1934) list trauma, heat and infection as factors in the production of physiological anastomoses in the rabbit's ear, Bean (1945) records hepatic disease and pregnancy as probable and vitamin deficiency as possible factors in the development of the cutaneous arterial spider.

The recent extensive literature on pulmonary arteriovenous aneurysms has shown that the most important etiological factor is an inherited predisposition to this disease, as in 100 cases 14 patients have given a family history of cutaneous vascular defects, 6 of epistaxis, and 4 of cyanosis, while twice the lesion has occurred in brothers. Other evidence which suggests that the disease may be an aberrant form of hereditary telangiectasis is the finding of superficial vascular lesions in 42 per cent. of patients and its discovery in patients who have typical Rendu-Osler disease (Garland and Anning (1950).

There is no evidence that the onset of the disease is influenced by pregnancy or puberty, but in ten patients the first symptoms were noticed during an acute respiratory infection, while three patients were found to have pulmonary tuberculosis. Possibly a respiratory infection may first unmask a

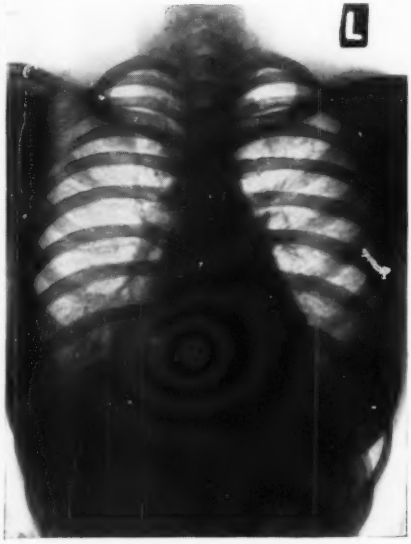

FIG. 1.—A large vascular anomaly is present at the right base, with multiple small loops in the left upper zone.

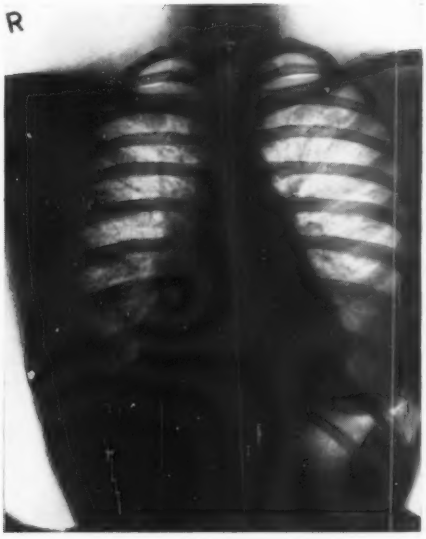

FIG. 2.—The further development of the lesion, with opacities in the left upper zone resembling tuberculous infiltration.

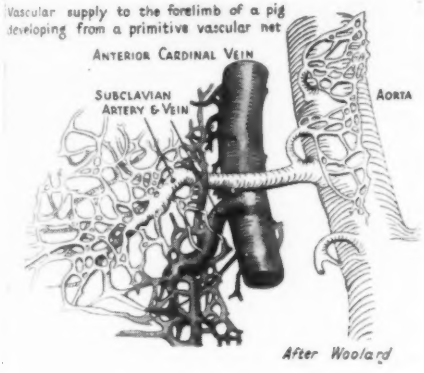

FIG. 3.—(After Woolard.) The developing subclavian vessels in the forelimb of the pig, showing numerous communications between artery and vein.

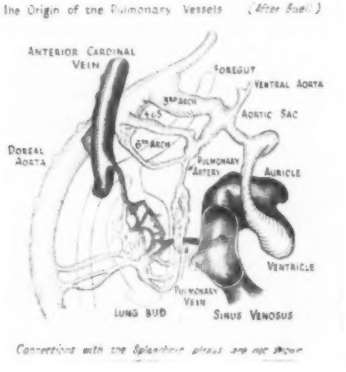

FIG. 4.—(After Buell.) The vascular supply of the embryonic lung, showing the arteries arising from the dorsal and ventral aortae and the veins draining into the sinus venosus and the anterior cardinal veins.

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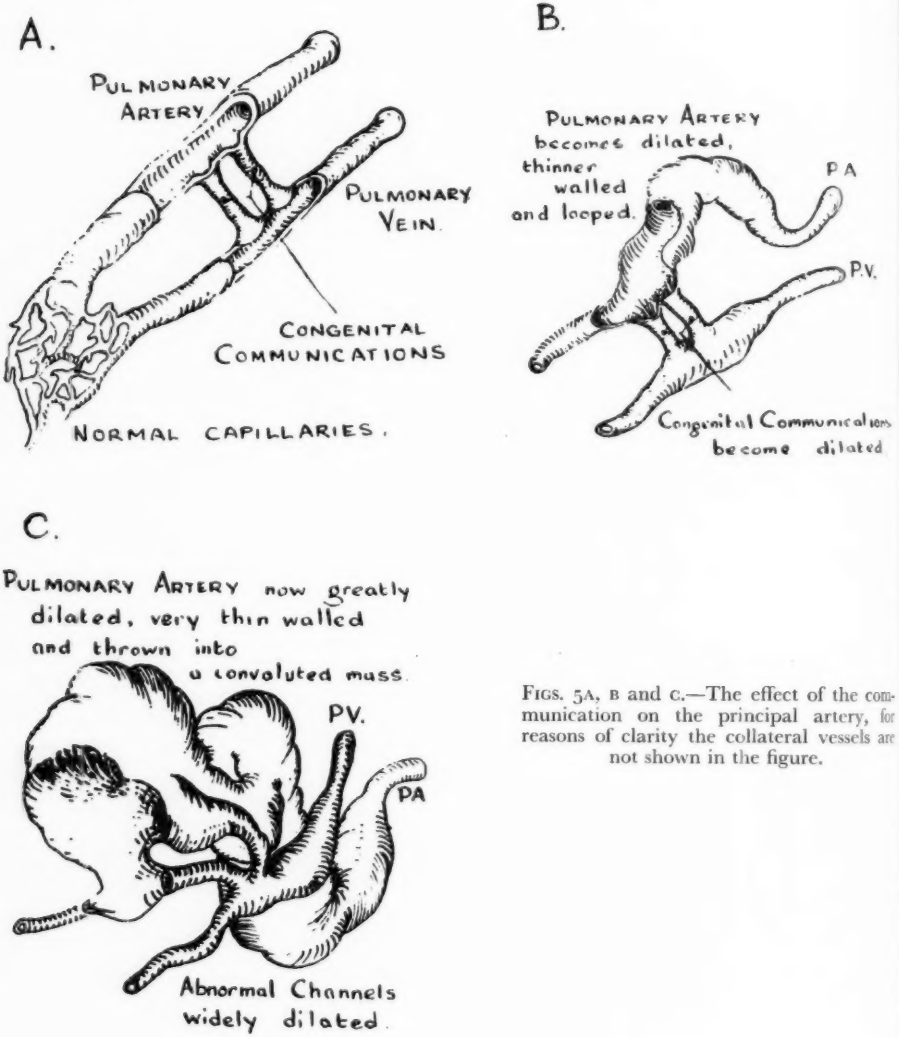

FIGS. 5A, B and C.—The effect of the communication on the principal artery, for reasons of clarity the collateral vessels are not shown in the figure.

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latent cyanosis rather than act as a stimulating factor in the development of the disease.

The Origin of the Lesion.—The congenital theory of vascular anomalies or Baadar-Krause law (Woollard 1922) helps to explain not only the origin of these lesions but also the absence of symptoms in some cases, as is shown by the study of the development of the blood supply to the lungs.

The lungs are developed as an outgrowth of the foregut and the primitive lung buds are permeated by solid cords of angioblasts which have sprouted from the regional vessels — namely, the ventral and dorsal aortæ and the anterior cardinal veins. These solid cords soon undergo a central softening to form the capillary net, and by the selection and development of certain pathways in this network the primitive arteries and veins are formed. These early vessels have a retiform structure and possess somewhat free communications between the arteries and veins, as is well shown by Woollard (*loc. cit.*). (Fig. 3.) These early arteriovenous anastomoses are normally obliterated, but if they persist they would form the basis of a pathological arteriovenous aneurysm, as was first pointed out by Sabin in a letter to Halsted (1917).

Since these lesions arise from a defective development in the adaptive phase—*i.e.*, after the formation of the vascular net—the term "arteriovenous aneurysm" is preferred to that of hæmangioma, which suggests that the lesion is a blastoma and therefore arises from cells sequestrated during the phase of angioblastic proliferation.

In its permanent form the pulmonary artery arises from the ventral aortic sac and the pulmonary vein is incorporated into the dorsal wall of the sinus venosus. Normally the connections with the anterior cardinal veins disappear and those with the dorsal aortæ persist only as the bronchial arteries. (Fig. 4.)

Possible arteriovenous connections are therefore as follows: between a pulmonary artery and a pulmonary vein, a pulmonary artery and an abnormal pulmonary vein draining to a systemic vein (a persistent cardinal connection), a bronchial artery and a normal or abnormal pulmonary vein or, finally, the coronary vessels may be involved. The usual connection is between pulmonary artery and pulmonary vein, and this alone provides the shunt between the right and left sides of the heart necessary for the production of cyanosis. Grishman (1947) has described a lesion from which an abnormal pulmonary vein drained into the inferior vena cava, while Biork and Crafoord (1947) record an instance where a coronary artery gave a branch to the lesion. Several instances of enlarged bronchial arteries are given but none in which this artery was the main feeder to the lesion.

The Development of the Lesion.—The opening of the arteriovenous shunt causes a fall in the diastolic blood pressure in the artery proximal to the shunt. This fall in pressure causes blood to be diverted from the next more centrally placed artery, a process which can reach the heart itself provided that at each arterial bifurcation a sufficiently large proportion of blood is diverted towards the lesion. This fall in arterial tension leads to a thinning of the arterial walls in accordance with the second histomechanical principle of Thoma (1893), but as these thin-walled vessels have to transport an in-

creased volume of blood with a high pulse pressure they quickly become dilated, elongated and tortuous, as was noted by Hunter (1764). This process can progress until the artery thrown into larger and larger loops becomes a convoluted mass. (Fig. 5 a, b, c.) Another result of the fall in diastolic pressure is that blood is diverted towards the lesion from anastomotic vessels, and therefore such lesions frequently possess more than one feeder artery. The anastomotic vessels being subject to tensions similar to those of the parent artery also become dilated and tortuous, and because of the high pulse pressure pulsate vigorously—thus Bell's "congeries of active vessels" is formed.

The lesion varies in the number and size of its connections between the artery and vein, the size of the vessels involved and the number of its anastomotic tributaries. Those lesions connecting the smallest and most peripheral vessels are known as superficial telangiectasia, those connecting slightly larger vessels and having abundant anastomotic tributaries are called circoid aneurysms, while those connecting large vascular trunks and having few anastomotic tributaries are known as arteriovenous aneurysms.

The pulmonary veins do not appear to be affected by the shunt to the extent found in the systemic circulation. This is probably because the pressure gradient between artery and vein is less and the elastic tissue of the lung provides better support.

Unfortunately on section both an arteriovenous and a circoid aneurysm may be mistaken for a cavernous hæmangioma, and as pointed out by Drysdale (1904) it is only by tracing the feeder artery into the lesion that a correct diagnosis can be made.

Because this lesion grows as a tissue in response to histomechanical tensions and not as an independent cell mass Adami (1909) states, "these lesions are not blastomas and should be classified as telangiectases rather than as angiomas." This is certainly true, but the term "arteriovenous aneurysm" is preferred because it is the modern equivalent of Bell's "aneurysm from anastomosis" and similarly stresses the basic anastomotic defect.

Summary

A case of arteriovenous aneurysm in the lung has been described, the development of which was followed by means of serial skiagrams. The structure as revealed by this method is similar to that displayed by casts and dissection.

It is considered that superficial telangiectasis, circoid aneurysm and arteriovenous aneurysm are different manifestations of essentially the same developmental anomaly. They are not hæmangiomata as they do not arise directly from primitive angioblastic tissue and possess no power of independent cell growth, but develop as a vascular tissue in response to mechanical tensions. The term "arteriovenous aneurysm" is preferred for historical and descriptive reasons.

I wish to thank Dr. Walton for allowing me to study this case and Dr. Foreman for lending me the Brompton Hospital notes, X-rays and the post-mortem report. I have to thank many friends, both colleagues and patients, at Broomfield Hospital for translations and illustrations. Finally, I wish to thank Dr. T. S. L. Beswick of the Department of Pathology of Cambridge University for reading the manuscript and Dr. Philip Ellman for his helpful criticisms.

REFERENCES

ADAMI, J. G. (1909): "The Principles of Pathology," Vol. I, p. 749, Oxford Medical Publications, London.

BAADER, A. (1866): "Ueber die Varietäten der Armarterien des Menschen und ihre morphologische Bedeutung," p. 33, Rieder and Simmen, Bern.

BEAN, W. B. (1945): *Medicine*, Baltimore, **24**, 243.

BELL, J. (1801): "The Principles of Surgery," Vol. I, Cadell and Davies, Edinburgh.

BJÖRK, G., and CRAFOORD, C. (1947): *Thorax*, **2**, 65.

BOWERS, W. F. (1936): *Neb. St. Med. J.*, **21**, 55.

CLARK, E. R., and CLARK, E. L. (1934): *Amer. J. Anat.*, **55**, 407.

DRYSDALE, J. H. (1904): *Trans. Path. Soc. Lond.*, **55**, 66.

GARLAND, H. G., and ANNING, S. T. (1950): *Brit. Med. J.*, **1**, 700.

GOLDMAN, A. (1948): *Amer. Rev. Tuberc.*, **57**, 266.

GRISHMAN, A., POPPEL, M. H., SIMPSON, R. S., and SUSSMAN, M. L. (1949): *Amer. J. Roentgenol.*, **62**, 500.

HALSTED, W. S. (1919): *Proc. Nat. Acad. Sci., Wash.*, **5**, 76.

HAYWARD, J., and REID, L. (1949): *Thorax*, **4**, 137.

HEPBURN, J., and DAUPHINEE, J. A. (1942): *Amer. J. Med Sci.*, **204**, 681.

HOLMAN, E. (1937): "Arteriovenous Aneurysm," Macmillan, New York and London.

HUNTER, W. (1764): *Med. Observations and Inquiries*, **2**, 390.

KRAUSE, W. (1868): "Handbuch der systematischen Anatomie des Menschen" (Henle), Vol. III, p. 204, Vieweg u. Sohn, Braunschweig.

LERICHE, R. (1949): "Aneurysmes artériels et Fistules arterio-veineuses," Masson, Paris.

LINDSKOG, G. E., LIEBOW, A., KAUSEL, H., and JANZEN, A. (1950): *Ann. Surg.*, **132**, 591.

READING, B. (1932): *Tex. St. J. Med.*, **28**, 462.

RODES, C. B. (1938): *J. Amer. Med. Ass.*, **110**, 1914.

SMITH, H. L., and HORTON, B. T. (1939): *Amer. Heart J.*, **18**, 589.

TAUSSIG, H. B. (1947): "Congenital Malformations of the Heart," p. 40, Commonwealth Fund, New York.

THOMA, R. (1893): "Untersuchungen über die Histogenese und Histomechanik des Gefässsystems," Enke, Stuttgart.

WHITAKER, W. (1947): *Thorax*, **2**, 58.

WILKENS, G. D. (1917): *Beit. Klin. Tuberk.*, **38**, 1.

WOOLLARD, H. H. (1922): *Cont. Embryol. Carneg. Instn.*, **14**, 139.

ELECTRICAL CONVULSIVE THERAPY IN PSYCHIATRIC PATIENTS WITH PULMONARY TUBERCULOSIS

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Pulmonary tuberculosis has generally been regarded as one of the main contra-indications to electrical convulsive therapy. Sargant and Slater (1948), referring to the risks of E.C.T., state without further comment that the lighting up of old tuberculous conditions has been reported, and Kraines (1948) remarks that "only in cases of actual tuberculosis of the lungs does it appear that the dangers of shock treatment are very great." In assessing the risks of E.C.T., the possibility of activating old-standing tuberculosis has usually been to the fore, and especially if a case presented a history of recent hæmorrhage or activity convulsive therapy tended to be withheld. However, Jentoft (1949), studying fifty-six tuberculous mental patients (of whom twenty were suffering from a destructive lesion), found that in thirty-five of his cases there was no change in the pulmonary condition following E.C.T. His valuable report unfortunately contains few detailed case histories of the pulmonary disease, which are needed in order to clarify the practical problems of clinical assessment. In addition, the place of convulsive therapy in the treatment of psychiatric patients who are suffering from pulmonary tuberculosis has to be reconsidered in the light of the advantages conferred by the increasing use of muscle relaxants for the modification of the actual convulsion of E.C.T. and the advent of the newer chemotherapeutic remedies for tuberculosis. The utilisation of these advances in technique and therapy is illustrated in the following cases.

Case 1

F. R. A. C., male, unmarried, aged 32, was admitted to mental hospital on December 13, 1951. He was an only child and the family history contained nothing of importance. There was nothing relevant in the account of his early life. His school record was good, and in November 1939 he took up male nursing in a tuberculosis sanatorium and subsequently remained employed in this type of work.

In May 1938 he complained of a cough, night sweats and general lassitude. An X-ray of the chest, taken in the same month, showed a large cavity in the right lower lobe. The sputum was reported to be positive for tubercle bacilli. He was admitted to a sanatorium in July 1938 and a right artificial pneumothorax was induced. He remained confined to strict bed-rest for a month, and subsequently he was allowed to get up for progressively longer periods. His condition became quiescent and he was discharged from the sanatorium and remained employed for the following seven years, the only treatment he received being periodic refills for his pneumothorax. In 1946 X-ray of his chest showed some infiltration on the left side, and three successive sputum examinations, taken at weekly intervals, were positive for

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tubercle bacilli. He was again confined to strict bed-rest, this time for twelve months, and was subsequently being allowed up for gradually increasing periods when he developed an effusion on the right side. Strict bed-rest was resumed for a further twelve months and this was supplemented by aspiration of the effusion on three occasions. His condition improved again, and in August 1948—when he was getting up for four hours per day—he was discharged home in order to complete his convalescence. By the spring of 1949 he was getting up for whole days, but in July 1949 the effusion on the right side flared up again. He remained in bed at home (apart from getting up to go to the toilet) for another twelve months, and during this time he became "very harassed and upset . . . fed up and depressed," and was having difficulty in sleeping. At his own request he was readmitted to the sanatorium in the summer of 1950. Two months later he was again getting up for whole days and he was discharged home in July 1951. However, after only two months at home there was a further flare-up of the effusion on the right side. Aspiration of the effusion was performed, and in October 1951 the patient was again admitted to a sanatorium. His depressive symptoms became more marked and a psychiatric opinion was sought, as a result of which he was admitted (on December 13, 1951) as a voluntary patient to a mental hospital.

On admission to mental hospital he stated, "It's just that I feel depressed about my lung trouble." In July 1951 he met a girl and he had hopes, "with medical sanction, of marrying some day." Since being readmitted to hospital his confidence had been shattered. "I just don't seem to have any bright outlook," he said. "What's the use?" He was in good contact, not retarded, and gave a very intelligent account of himself. (Progressive Matrices Intelligence Test: Gr. I.) He looked miserable and depressed. His sole topic of conversation was his physical condition and he felt his future was completely hopeless. ("I seem to have no fight in me . . . I feel depressed. Just feel I've lost sort of hope. What's the use of it all?") He added spontaneously that he knew his physical condition was not, in fact, sufficiently severe to justify his mental attitude, but that, in spite of this knowledge, he was quite unable to alter his outlook. ("I just can't shake myself out of it. I feel awful. I'm so depressed. I can't do a thing. It's terrible.") He was unable to concentrate on simple occupational tasks and he had frequent bouts of weeping. His most persistent complaint concerned his "utter lack of any desire to do anything . . . I seem to have lost all my go." He did not, however, express suicidal ideas and there was no evidence of other psychotic thinking. He was considered to be suffering from an affective psychosis, his condition being essentially a depressive reaction to his pulmonary tuberculosis.

Though the patient's psychiatric disorder was regarded as presenting an indication for electrical convulsive therapy, it was felt that, in view of his pulmonary condition, methedrine therapy should be tried in the first instance. He was therefore treated with tabs. methedrine (desoxyephedrine), 2·5 mgm. given before breakfast, and the dosage was raised by 2·5 mgm. every third day until he was receiving 10 mgm. at 7 a.m., 10 a.m. and midday respectively (Rudolph, 1949). However, there was no response to this therapy, and the question of administering E.C.T. became more pressing. A chest X-ray soon after admission to mental hospital showed "hydro-pneumothorax on the right side and some calcified foci on the left side." The E.S.R., taken at intervals of four days, varied between 25 and 35 mm. after one hour. Weekly sputum examinations were negative for tubercle bacilli. One month after

admission a further X-ray film was taken, and the opinion of the visiting Chest Physician was that there was no evidence of activity in the left lung and that the right lung showed marked pleural thickening over the lower lobe with resolution of the encysted effusion over the upper lobe. These findings were balanced against the severity and persistence of the patient's psychiatric symptomatology, and it was finally decided to administer a course of E.C.T., modifying the convulsions by the use of a relaxant and employing streptomycin and sodium *p*-aminosalicylate (P.A.S.) as protective measures against the possible flare-up of the tuberculosis.

Thirty minutes before each electrical treatment the patient was premedicated with an intramuscular injection of $\frac{1}{75}$ gr. of atropine. Immediately prior to the treatment 120 mgm. of a 4 per cent. solution of flaxedil (gallamine triethiodide) was mixed with 0·25 g. of pentothal and administered intravenously by an anæsthetist. Oxygen was given via a Boyle's apparatus for 120 seconds, a mouth gag was inserted and the electrical treatment was then given. When the softened convulsive movements ceased an air-way was passed, an oxygen-carbon dioxide mixture administered, and 4·5 mgm. of prostigmine injected intravenously in order to antagonise the effect of the flaxedil. The patient received eight applications of E.C.T., given twice weekly. Throughout the course he was confined to bed (apart from attending the toilet, and being conveyed to the treatment room on a wheel-chair) and given 1 g. of dihydrostreptomycin intramuscularly daily, and 3 g. of sodium P.A.S. five times daily by mouth.

Following the course of E.C.T., he made an impressive recovery from his depressive state. He became cheerful, smiled freely and was no longer exclusively preoccupied with his pulmonary condition. Though he did not underestimate the latter, there was an air of optimism about him, and he expressed the hope that he might become fit enough to resume work and marry. An X-ray of his chest, taken a few hours following the last application of E.C.T., showed "no change" in his condition, and the Chest Physician who examined the patient two weeks later found no clinical evidence of activity. After a further interval of one month a tomogram was taken, and again there was no change to report. The E.S.R. varied from 25 mm. to 35 mm. (after one hour) and the sputum remained negative for tubercle bacilli. The patient was allowed out of bed daily for gradually increasing periods and was subsequently encouraged to attend the occupational therapy department and to take part in the various social activities arranged for the patients in the hospital. He continued to progress uneventfully and was finally discharged on June 10, 1952, and placed under the supervision of the Chest Physician at the local clinic.

Soon after his discharge the patient resumed work as a male nurse in a hospital for infectious diseases and tuberculosis. The report from the Chest Physician (August 29, 1952) stated: "Since his discharge he has kept well and settled down happily. . . . The last X-ray of his chest showed the right lung fields to be almost obliterated by dense pleural thickening. . . . General condition good." On September 4, 1952, the patient was seen (by the writer) for a follow-up interview. He was quite cheerful and felt "wonderfully well." He was working for thirty hours per week and leading "a virtually normal life." He was receiving no special treatment and was extremely grateful for the progress he had made. He hoped to marry in due course.

Case 2

L. E. H., male, married, aged 57, was admitted to mental hospital on

June 3, 1952. He had a happy childhood, attended school from age 5 to age 14, and after leaving school he worked as a truck driver. He remained employed as a truck driver, apart from an interval of four years when he served in the 1914-18 war and was "gassed" in France. He married at the age of 25, became the father of three healthy children, and the marital relationship was a happy one.

In 1940, when aged 45, he was admitted to a mental hospital suffering from an endogenous depressive psychosis. He had made a suicidal attempt by gassing and, in addition to being depressed, he was markedly hypochondriacal. He was treated by a course of electrical convulsive therapy and made a good recovery. There was no other history of ill-health, either physical or psychiatric, and there was nothing relevant in the family history.

The patient returned to normal employment and remained quite well until approximately one year prior to his recent admission to a mental hospital. During this year he gradually became more depressed, lost appetite and developed hypochondriacal ideas. On March 13, 1952 (*i.e.*, three months prior to admission), he had a hæmoptysis and coughed up approximately one cupful of blood. He was referred to a Chest Hospital and, at that time, X-ray of the chest showed bilateral upper zone tuberculous infiltration, and cavitation in the right mid-zone was queried. There was little cough, but the sputum was reported to be positive for tubercle bacilli. On the advice of the Chest Physician the patient stopped working and—apart from a monthly visit to the Chest Hospital—he remained in bed at home, pending his admission to a sanatorium. No other treatment was prescribed. Meanwhile, however, his psychiatric symptoms became more marked. His depression increased in severity, he had difficulty in sleeping and became progressively more self-absorbed. As a result he was admitted to a Psychiatric Observation Unit on June 3, 1952, and subsequently transferred (on June 11, 1952) as a voluntary patient to a mental hospital.

On admission he complained of dryness of the mouth, lips and tongue, insomnia, loss of appetite and depression. He stated that when he emerged from a bath the water immediately "ran off" him so that there was hardly any need for him to dry himself. ("As though you've dipped in grease first. . . . It must be something inwardly.") He looked extremely miserable and dejected but was not retarded. Though the facial expression was not fixed he was unable to smile and was preoccupied with his symptoms. There was no evidence of frank suicidal tendencies, though he did state that he felt his condition was very similar to the one from which he suffered in 1940. He was unable to give any obvious cause for his depression. (Progressive Matrices Intelligence Test: Gr. III+.) He was considered to be suffering from a recurrence of his depressive psychosis.

On June 13, 1952, the E.S.R. was 15 mm. after one hour. X-ray of the chest (June 16, 1952) showed "infection of both sides in upper and middle zones." The sputum (June 17, 18 and 19, 1952, and at weekly intervals following) showed no evidence of tubercle bacilli. The patient remained extremely depressed, self-absorbed and preoccupied with his symptoms, and it was considered that, from the psychiatric viewpoint, there was a strong indication for electrical convulsive therapy. The Chest Physician was consulted and, in his opinion, the latest X-ray showed some resolution of the disease as compared with the original X-ray taken at the Chest Hospital. In view of the severity of the patient's psychiatric disorder it was therefore decided to proceed with E.C.T. In this case a short-acting synthetic muscle relaxant was used to modify the convulsions and the whole course of treatment was given

under an "umbrella" of streptomycin and sodium P.A.S. (The doses of these drugs were the same as in Case 1.)

The patient was premedicated with $\frac{1}{75}$ gr. of atropine, and thirty minutes later 0·25 g. of pentothal was given intravenously. Seventy mgm. of scoline (succinylcholine chloride) was then injected intravenously from a separate syringe, the dosage being based on the patient's body weight. Oxygen was given via a Boyle's apparatus for approximately forty-five seconds, a mouth gag was inserted and the electrical treatment was administered. Following the softened convulsive movements, an air-way was passed, and oxygen was given for a short time until normal breathing was re-established. As in Case 1, the patient was virtually confined to bed throughout the course of treatment, which consisted of ten applications of E.C.T. given twice weekly.

The patient made a good recovery from his psychotic state. He was no longer depressed or hypochondriacal. ("I feel a king to what I was.") He was able to sleep satisfactorily and could concentrate on occupational therapy during the day. He looked forward to returning to normal work. An X-ray of his chest, taken two days following the last application of E.C.T., showed "no appreciable change" in his condition. The E.S.R. remained at 15 mm. after one hour and no tubercle bacilli were discovered in the sputum. In view of his insistent desire to leave hospital, he was discharged (rather earlier than was wished) two weeks after completing the course of E.C.T. and referred back to the Chest Hospital.

Two weeks later a report from the Chest Hospital stated that "his general condition had considerably improved . . . and his X-ray picture showed some clearing. Tomographs showed no definite cavitation and his sputum was negative." A further report received after an interval of two months stated that he had been seen by the Chest Physician for the third time since his discharge from mental hospital and that "the considerable improvement in the X-ray appearance of his lungs" had been maintained.

Discussion

Depressive reactions associated with pulmonary tuberculosis are not an uncommon occurrence. The diminished appetite and general physical deterioration which result from depressive symptomatology have an adverse effect on the pulmonary condition and a true vicious circle is set up. The successful treatment, therefore, of the depressive symptoms is also likely to benefit the accompanying physical disorder.

Rudolph (1949) reported the results of treating forty-two cases of depression with desoxyephedrine. He found that the percentage of improvement was identical with that in a similar series treated with E.C.T. In view of the obvious advantages of treatment by tablets in sufferers from pulmonary tuberculosis Case 1 was given, in the first instance, a course of desoxyephedrine. However, in common with the general findings of Monro and Conitzer (1950), the response to this form of therapy was poor. They concluded that "where electroshock is reasonably well indicated, there is little reason to consider desoxyephedrine as a possible alternative." They found that the main use of the latter was in depressive states which were considered to have a poor prognosis with E.C.T.

Close (1949) treated with E.C.T. eight psychotics (seven schizophrenics and one involutional melancholia) who were suffering from "active pul-

monary tuberculosis." In each case the tuberculous condition, judged by X-ray controls, showed improvement following the course of convulsive therapy. In the present report Case I in particular appeared to make striking progress following E.C.T. Though he had been off work because of his tuberculosis some five years previously, on discharge from mental hospital he was able to return to a normal, active working life. It was difficult to resist the impression that convulsive therapy had broken the vicious circle already described and was an important factor responsible for his physical, in addition to his psychological, progress. Also, in Case 2, though the sputum was positive for tubercle bacilli three months prior to starting E.C.T., it subsequently became negative and remained negative for tubercle bacilli during and following the course of convulsive therapy. Close states that, theoretically, E.C.T. might be expected to have an untoward effect upon latent and active pulmonary tuberculosis because the induced convulsion is characterised by a maximal forced inspiration and terminated by a forced expiration, thereby introducing the possibility of tearing fibrous patches containing tubercle bacilli. However, the use of muscle relaxants tends to reduce, if not actually eliminate, these hypothetical adverse mechanical risks, and the prophylactic administration of the newer chemotherapeutic remedies for tuberculosis provides a further protective barrier against the spread of the tuberculous process.

Karliner and Savitsky (1951) used curare-controlled E.C.T. in the successful treatment of a depressed patient suffering from active pulmonary tuberculosis, each treatment being preceded by a pneumothorax. Kaldeck *et al.* (1948) also suggested that, if there is a recent history of hæmorrhage, E.C.T. should be given only if the pulmonary process has been controlled by collapse therapy. It is of interest to point out, therefore, that in Case 2 of the present report the patient had a hæmoptysis three months prior to commencing E.C.T., and though collapse therapy was not initiated, no untoward effects were observed following a course of scoline-modified E.C.T.

Other workers have commented on and discussed the effect of E.C.T. on latent or active pulmonary tuberculosis (*e.g.*, Hemphill, 1942; Kino and Thorpe, 1946; Will and Duval, 1947; Jentoft, 1949), but they were not employing relaxants for the modification of the actual convulsion of E.C.T. In the cases reported here relaxants were used, in addition to chemotherapy, in order to prevent an adverse effect on the pulmonary infecton. (Further experience, of course, may show that, with adequate softening of the fit, there is no necessity to supplement the treatment with chemotherapy.)

Summary

Two cases are described in which subjects of pulmonary tuberculosis developed depressive states and were treated with E.C.T. under an "umbrella" of sodium P.A.S. and streptomycin, the convulsions being modified by the use of muscle relaxants. In each case no untoward effects were observed on the physical condition, which in fact progressed favourably. It is hoped that these case histories may contribute towards the clarification of the practical problems of clinical assessment.

It is a pleasure to thank Dr. J. S. Harris, Physician-Superintendent, Claybury Hospital, for permission to utilise the clinical material and records of the hospital, and Dr. H. Duff Palmer, Physician-Superintendent, Harts Hospital, who advised on the treatment of the chest conditions.

REFERENCES

CLOSE, H. P. (1949): *Am. J. Psychiat.*, **106**, 352.
HEMPHILL, R. E. (1942): *Lancet*, **2**, 152.
JENTOFT, B. (1949): *J. Ment. Sci.*, **95**, 651.
KALDECK, R., *et al.* (1948): *New England J. Med.*, **239**, 778.
KARLINER, W., and SAVITSKY, N. (1951): *Dis. Nerv. System*, **12**, 186, quoted, "Progress in Neurol. and Psychiat." (1952), vol. vii, p. 557. Ed., E. A. Spiegel. Grune and Stratton, New York.
KINO, F. F., and THORPE, F. T. (1946): *J. Ment. Sci.*, **92**, 138.
KRAINES, S. H. (1948): "The Therapy of the Neuroses and Psychoses," 3rd ed. London: Henry Kimpton.
MONRO, A. B., and CONITZER, H. (1950): *J. Ment. Sci.*, **96**, 1037.
RUDOLPH, G. DE M. (1949): *J. Ment. Sci.*, **95**, 920.
SARGANT, W., and SLATER, E. (1948): "An Introduction to Physical Methods of Treatment in Psychiatry," 2nd ed. Edinburgh: Livingstone.
WILL, O. A., and DUVAL, A. M. (1947): *J. Nerv. and Ment. Dis.*, **105**, 637.

REVIEWS OF BOOKS

B.C.G. Vaccination. Studies by the W.H.O. Tuberculosis Research Office, Copenhagen. 1953. World Health Organization, Geneva. Pp. 307. 15s. $3.00. Sw. fr. 12. Fr. fr. 960.

This Report is No. 12 of the World Health Organization series and has been prepared under the direction of Dr. Lydia B. Edwards, Chief of Field Studies, Dr. Carroll E. Palmer, Director, and Knut Magnus, Assistant Statistician. The investigations were undertaken under the joint auspices of the International Campaign, the Danish State Serum Institute, and the W.H.O. Tuberculosis Research Office, and were the outcome of many discrepancies in results and reactions which came to light at the Conference on European B.C.G. Programmes which was convened in September 1949. It was obvious that these discrepancies were substantial and that the answer to them, and to other fundamental problems, would not be found by discussion. The monograph sets out the work done during the first three years of the research programme, from November 1949 to September 1952, and the authors state that while some of the findings can only be viewed as preliminary and the conclusions as tentative, many are founded on solid foundations. As many of the findings differ from current views on B.C.G., they are of practical interest at the present time when the vaccine is beginning to be used widely in Great Britain.

The subjects of study were: storage of vaccine at different temperatures; exposure of vaccine to light; effects of diluting vaccine; dead (heat-treated) vaccine; variations in preparation of vaccine; variations of technique of intracutaneous injection of vaccine; response at different intervals after vaccination; and comparison of vaccines from different production centres. More than 40,000 school children in four different countries (Denmark, Egypt, Southern India and Mexico City) were tuberculin-tested, and more than half of the number (23,000) were vaccinated in the course of twenty-seven separate studies in which varying combinations of different vaccines, techniques and vaccination conditions were employed.

The method of tuberculin-testing used was the standard intracutaneous one, and methods and dilutions employed are detailed. Results are shown as histograms which demonstrate, the authors claim, the existence of two different types of tuberculin sensitivity, one high grade and the other low grade, the latter type being fairly prevalent in Southern India and very prevalent in Egypt. They state grounds for their belief that this type "constitutes a non-specific response to tuberculin the cause of which is still unknown." It is, they say, the result of something other than infection with *Mycobacterium tuberculosis*, human or bovine type, and is closely associated with "geographical factors." If this observation is correct it has important implications, but more conclusive proof is obviously required.

A chapter is devoted to discussion of the response to vaccination. No correlation between the size of the B.C.G. papule and the post-vaccination reaction could be determined in any of the series of investigations. Two chapters are devoted to variation of factors which might affect allergenic properties and explain the varying levels of post-vaccination allergy which characterised the international B.C.G. campaign. Storage of the vaccine at 2°-4° C. for up to four to five weeks had no appreciable effect, and a long period of

storage *per se* is required to effect deterioration. Variation of temperature, on the other hand, affects the vaccine sharply, and even short exposures to near body-heat may greatly reduce its power to produce allergy. Exposure to light causes even more rapid deterioration and a quick fall in the colony count. Transient exposures to light or to temperatures much above 20° C. may render the vaccine inert.

There is an interesting chapter on variations in the technique of intracutaneous injection. The difficulties of always giving the exact dose (0·1 ml.) into the exact layer of the skin are notorious, but quite large reductions in volume and strength of vaccine dilution were found to have little effect on resulting skin sensitivity. On the other hand, the size of the local lesions varies directly with the depth of injection and complications are more frequent with deeply given injections.

Variations in certain manufacturing stages and techniques had no effect on the resulting vaccine, but batches from one laboratory often differed appreciably from one another and very greatly from those from other laboratories. This question is discussed in detail. A final interesting chapter deals with the effects of varying the numbers of dead and living bacilli in the vaccine. An increasing number of dead organisms affects the development of allergy much more than the capacity to produce local lesions, and by the variation of these two constituents, living and dead, vaccines which are qualitatively quite different can be produced. The obvious importance and significance of this finding are discussed. Appendices of tables cover 150 pages.

It may be that B.C.G. work has become too easy largely because so much of it can be delegated, and the routine of one day tends to merge into that of the next. Observing and thoughtful physicians have always seen the problems. They will find answers to many of them in this carefully produced report, which should be studied attentively by all who have to do with this important prophylactic work.

CHARLES CAMERON.

Thoracic Surgical Management. By J. R. BELCHER and I. W. B. GRANT. With a foreword by Sir Clement Price Thomas. Pp. x + 196. Baillière, Tindall and Cox. 16s.

This excellent book, designed for residents in thoracic units and for those having occasional care of thoracic surgical cases, is born of practical experience. In his preface Sir Clement Price Thomas very rightly remarks that it fills a long-felt need.

The newcomer to thoracic surgical work finds himself in a very strange land—in the past he has turned in vain to textbooks for guidance. In the volume under review he will find wise and practical guidance on all the day-to-day problems which beset him, and which, as the authors state, have previously been taught by precept and example.

The scope of the volume is most comprehensive and includes up-to-date information on the surgery of mitral stenosis, as well as on other aspects of cardiac surgery.

Common topics are fully dealt with and include excellent sections on bronchography, artificial pneumothorax, aspiration of the pleura, etc. The chapter on thoracoplasty is particularly comprehensive and provides evidence that the authors have not relegated this well-tried operation to the "condemned cell"!

Finally, one or two minor criticisms. On p. 76 the figure illustrating sites

of obstruction in drainage tubes might well include the tapering glass connection so well beloved of many ward sisters. On p. 82 in dealing with technique of dilatation of an empyema sinus, air embolism is cited as a complication but no mention made of cerebral embolism from infected clot, nor of the wisdom of employing an antibiotic " umbrella " during such a dilatation. On p. 100 the occasional occurrence of contralateral spontaneous pneumothorax after pneumonectomy might well be included in the list of complications of this operation. In the treatment of pulmonary œdema following pneumonectomy the vital necessity for mechanical removal of secretions from the bronchial tree is not mentioned. The information on the technique of angiocardiography is placed under the heading of Fallot's Tetralogy—it might be better separated from this, as it has now so many applications to other aspects of thoracic surgery. In a future edition a section on the place and value of early ambulation in thoracic surgery might with benefit be included. The table of nomenclature of the bronchial tree on p. 18 contains an error—the apical and anterior bronchi of the right upper lobe in the international nomenclature are reversed in position.

These are, however, only minor criticisms in a book which I read with the greatest pleasure, and which will become to the thoracic surgical resident what another well-known manual of general surgical handicraft has become to generations of general house surgeons.

GORDON CRUICKSHANK.

Tuberculosis in the Commonwealth. By N.A.P.T. Transactions of the Third Commonwealth Health and Tuberculosis Conference, July 1952. Pp. 441. Price 21s.

This is a full, verbatim report of the third Commonwealth Health and Tuberculosis Conference held in London in July 1952. In spite of its name only one-sixth of its four-hundred-odd pages is devoted to tuberculosis outside the British Isles, but these pages are among the most interesting. The magnitude of the problem faced by the less well developed territories is described by the delegates, few of whom have any reliable information in the form of mortality figures to help them decide just how great the problem is. Tuberculin-testing surveys, however, which do give some indication of the morbidity, show a high rate of positive reactors. It is also the impression of some workers that the ability to develop hypersensitivity is not always paralleled by development of resistance, the level of which in India, Pakistan and Africa is lower than that developed by Europeans. This makes one wonder how much is to be expected from the mass B.C.G. campaigns, some of which are already under way and which are said to be the only method of control within the means of these countries. It is clear from these papers, however, that, in spite of a crippling lack of trained staff, equipment and hospital beds, the problems are being faced with a growing awareness of their seriousness.

Dr. van Deinse outlined the policy and the law regulating compulsory vaccination with B.C.G. in France. The figures he quoted—over five million people already vaccinated in France and Morocco—were in sharp contrast to those of the two speakers from London who dealt in modest hundreds.

Most aspects of the management and control of tuberculosis in this country are covered in broad outline, and some in greater detail. The general practitioner's particular opportunities for observing the epidemiology

of the disease and assessing the needs of the patient are stressed by Dr. Dimmick. Encouraging figures for the results of domiciliary treatment are given by Dr. Peter Stradling, who spoke in reply to an uncompromising attack on this form of treatment, and pointed out that it necessarily filled a gap left by the shortage of beds.

In an interesting section on childbearing and tuberculosis, conflicting opinions were expressed and supported by analysis of clinical material.

This book contains material of interest to workers in every field of tuberculosis, not detailed accounts of any particular facet of the problem; but it presents in readable form, between the covers of a single volume, the points of view of clinicians, social workers and administrators.

K. D. YOUNG.

The White Plague. By RENÉ and JEAN DUBOS. London: Victor Gollancz. 1953. Pp. viii + 277. Price 15s.

The most notable achievement of the authors of this book is that they have written an account of tuberculosis which can be read with benefit by expert and layman alike. It is not too simple to be dismissed by the former as uninformative, nor too technical to be set aside by the latter as unintelligible.

The first part of the work deals with tuberculosis and the romantic age, with interesting but sombre biographical details of the geniuses who fell victims of the disease. Here we find the sad story of the Brontës and many others. But the authors are not impressed with the relationship of genius and tuberculosis, for "in the labouring classes consumption was not the aristocratic decline inspiring works of art. . . . It was the great killer and breeder of destitution." On this broader note the authors turn to Part II of this work.

This section deals with the growth of pathological knowledge culminating in the work of Villemin and Koch, and ends with a quite fascinating chapter on infection and disease. Part III concerns cure and prevention. The treatment of tuberculosis is surveyed from the time when cod-liver oil was the most potent remedy available to the present day. A warning footnote on Isoniazid (which had just appeared as the book went to press) must be quoted: "It is by causing *chronic* pulmonary disease that tubercle bacilli impose on society such a heavy burden of suffering and protracted death, and the control of this chronic disease is the real touchstone of anti-tuberculosis measures. There is as yet no evidence that the new drugs have satisfied this exacting criterion."

Part IV is entitled "Tuberculosis and Society." Epidemiology is made a very interesting study, especially as regards familial and racial susceptibility. The effects of the industrial revolution are graphically described and the growth of public participation in the anti-tuberculosis campaign. It is in connection with the last of these points that the book takes a strong American bias. To the British reader the absence of any reference to the work of Sir Robert Philip in developing the first co-ordinated tuberculosis scheme based on a central dispensary will seem very strange. The authors give credit to Lawrence F. Flick for a *programme* in Philadelphia, stated to be "the first of its kind in the world," which actually Sir Robert Philip had developed *and begun to practise* in Edinburgh in 1887.

CHRISTOPHER CLAYSON.

Traitement de la Tuberculose par l'Acide Para-Amino-Salicylique (P.A.S.). By J. PARAF, J. FOUQUET, P. ZIVY, J. DESBORDES, A. ABAZA, J. BORY and FOURNIER, E. PERETZ, MADELEINE PARAF and L. LÉVY. Paris: Masson et Cie. 1952. Price 3,200 francs.

It is already being forgotten that the introduction of para-amino-salicylic acid marked the beginning of a new epoch in the treatment of tuberculosis. It is true that chemotherapy had already been employed for this purpose, but the results of treatment were inconclusive and the substances themselves were potentially dangerous.

Para-amino-salicylic acid is relatively safe to prescribe and it has a considerable therapeutic action of its own.

It so happened, however, that we stood on the threshold of further discoveries. Before we had the opportunity of establishing P.A.S. in its proper place as a therapeutic agent we were presented in turn with streptomycin and isoniazid. The picture was temporarily obscured and the value of P.A.S. as a substance on its own has never been fully established.

It is therefore opportune that the facts with regard to P.A.S. should be collected and presented in a single volume such as this. Well written, well illustrated and well documented, it is well worth reading. It will also serve as a very useful work of reference.

It is interesting to note that, in this scientific work from France, the authors continue to refer to liquid measures in terms of cubic centimetres. The millilitre does not seem to have made an impression in the home of the metric system.

JAMES MAXWELL.

Tuberculose e Doenças do Aparelho Respiratório (Tuberculosis and Diseases of the Respiratory System). By Professor JOSÉ SILVEIRA and others. Bahia, Brazil. Pp. 456.

This book contains the writings of Professor Silveira and fourteen of his collaborators from Rio de Janeiro and Bahia. It covers almost the whole field indicated by its title; vaccination with B.C.G., including to the allergic, tuberculin hypersensitivity and its treatment, tuberculin diagnosis of tuberculosis among school children, the incipient pulmonary tuberculous lesion, bronchoscopic diagnosis, surgical treatment, antibiotics treatment in tuberculosis, and others.

In spite of the diversity of authors and subjects the material is presented with sufficient unity to have made its compilation in book form well worth while. It is probably due to the ability and sound knowledge of the editor, Professor Silveira, to whom the book owes its balance. His contributions on hypersensibility in tuberculosis and on cutaneous allergy are among the best in this compilation, particularly the second, which is an excellent study of this most important subject. I think this book is worth more than a perusal to all those interested in this subject.

J. TRUETA.

Review of Research in Tuberculosis. Vol. II. (Ergebnisse der gesamten Tuberkulosisforschung.) Edited by H. BEITZKE, ST. ENGEL, L. HEILMEYER and J. HEIN. Stuttgart: G. Thieme Verlag. 1953. Pp. 528. 240 figures.

This well-produced volume, appearing for the first time since the end of the second World War, endeavours to bridge the gap of pre-war and contem-

porary thought in tuberculosis. Little that is new regarding the pathogenesis of tuberculosis can be found and there are no references to the work by Florey and his school. The chapter by Uehlinger regarding the pathological anatomy of late pulmonary tuberculosis, in which macroscopic specimens are set opposite well-produced radiographs of the chest, is of interest. The author stresses the natural history and serial radiology of bronchial perforation by caseating lymph nodes and the subsequent aspiration metastases from that source. The histology is easy to follow and supplements the very clear description.

Of the other chapters, that by Wernli-Haessig, which covers modern management of pulmonary tuberculosis, deserves close perusal. The close-up views of the radiographs of the apices and the corresponding tomographs are excellent.

The international and Western literature is fairly well covered, but the German authors appear to be unfamiliar with the carefully conducted M.R.C. trials of the latest chemotherapy in pulmonary tuberculosis.

Report of the Congress of Tuberculosis of the East German Republic held at Leipzig, December 14-16, 1951. Edited by J. E. KAYSER-PETERSEN, Jena. Leipzig: J. A. Barth Verlag. 1952. Pp. 139. 91 figures.

This report affords valuable glimpses of the problems in management and prophylaxis of tuberculosis facing responsible workers in present-day Eastern Germany, Russia and Czechoslovakia. Delegates from these countries discussed chemotherapy of tuberculosis, and the views expressed were in accordance with orthodox principles and quite similar to those elsewhere. Schmelow of Moscow read an interesting paper on extra-pulmonary tuberculosis and the hepato-splenic syndrome. The author, by means of puncture biopsies, demonstrated small tubercles in the reticulo-endothelial system of the liver and spleen in early primary disease. This was frequently associated with a leucopenia. He regarded the splenic and hepatic foci, which occur in the early phases of the disease, as a sequel of a moderate bacteræmia, and advised the use of chemotherapy. Unless this is done these patients may in later life present with the so-called Banti syndrome, particularly after the primary disease has burnt itself out.

Fröhlich of Chemnitz, in an able review of industrial factors and tuberculosis, believes that the human factor, such as personal hygiene, was overwhelmingly more important in the dissemination of the disease than previous exposure to silica.

Schebanow of Moscow discussed P.A.S. and records the frequency of P.A.S.-resistant strains of tubercle bacilli on culture.

Knöll gave an account of the technicalities involved in the production of B.C.G. vaccines at the Jena laboratories. The products from this institute are now successfully used throughout Eastern Germany.

LEON CUDCOWICZ.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

Pulmonary Tuberculosis. By R. Y. Keers and B. G. Rigden. Edinburgh: E. and S. Livingstone, Ltd. Pp. 324. Illus. 150. 24s. net.

Brompton Hospital Reports. A Collection of Papers recently published from the Hospital. Vol. XXI, 1952. Published by the Research Dept. of the Hospital. Aldershot: Gale and Polden, Ltd. Pp. 206. Illustrated. 15s. net.

Health Horizon. Spring, 1953. N.A.P.T. Pp. 56, with Illus. Quarterly 2s. 6d.

Pathologie et Structure Pulmonaires. By H. Warembourg and P. Graux. Masson et Cie, Paris 6. Pp. 215. 2,500 Fr.

Probleme der Morphologie, Cytochemie und Wuchsform des Tuberkuloseerregers. By Dr. F. J. Bassermann. Stuttgart: Georg Thieme Verlag. Pp. 98, 40 Illus. DM 7.80.

Diseases of the Chest. By T. Royle Dawber and Lloyd E. Hawes. Baillière, Tindall and Cox. 1952. Pp. 458. 216 Illustrations. 76s. 6d.

The Classification of Pulmonary Tuberculosis. By Milosh Sekulich. William Heinemann. Pp. 322. 160 Illustrations. 63s.

Die Lungenresektionen. By Professor Dr. A. Lezius, with Foreword by Professor R. Nissen. VIII. Stuttgart: Georg Thieme Verlag. 1953. Pp. 143. 149 Illustrations. DM 49.80.

Pulmonary Tuberculosis. By W. Pagel, F. A. H. Simmonds and N. Macdonald. Oxford University Press. Pp. 742. Illus. 317. 84s.

Adjustment to Physical Handicap and Illness. A Survey of the Social Psychology of Physique and Disability. By Roger Barker, in collaboration with Beatrice A. Wright, Lee Meyerson and Mollie R. Gonick. Social Science Research Council, New York. Bul. 55, 1953. Pp. 440. Illus. 2. $2.

St. Thomas's Reports. Vol. VIII. 2nd Series. Pp. 148. Illustrated. 10s. 6d.

The Registrar-General's Statistical Review of England and Wales for the two years 1948-1949, Text, Medical. H.M.S.O. Pp. 370. 10s.

REPORTS

Health Review for 1951. Report of the Chief Medical Officer for the Ministry of Health.*

Sir John Charles in a reference to tuberculosis makes the following observations:

"There was a further considerable decline in *tuberculosis* deaths—fewer than 14,000 deaths from all forms, giving a rate of 315 per million living. This included a figure of 12,000 for respiratory tuberculosis, which represents a drop of over 2,000 on the previous year. An encouraging feature was that in the forty-four years since the introduction of the School Medical Service the crude death rate from all forms of tuberculosis among children had fallen by more than 90 per cent. both at pre-school and at school age."

Referring to the provision of sanatorium and hospital accommodation, both a curative and preventive measure, the Chief Medical Officer reports that month by month more nurses became available for sanatorium service and additional beds appeared in corresponding force. By these measures the waiting lists had been substantially reduced and the waiting period for admission shortened. But scarcity of nurses and surgeons experienced in thoracic surgery still prevented an early solution of the difficulties of obtaining treatment for those tuberculous patients recommended for thoracic treatment.

The epidemiological importance of the work of the mass miniature radiography units among the civilian population can scarcely be overrated, states Sir John, "for it is the unrecognised patient suffering from the active disease who spreads the infection in the community."

Of the total number of examinations (more than $2\frac{1}{4}$ millions) 94·8 per cent. showed no radiological evidence of the disease of the chest. Previously unsuspected active tuberculosis of the lungs was revealed in 3·5 per thousand and an average of 126 such cases were detected each week.

Sir John concludes that "it is impossible to register to qualified optimism with regard to tuberculosis . . . the end of the battle may appear to be in sight." But there were still some unsolved problems which required investigation and study "before the final attack is launched."

With regard to cancer of the lung, Sir John Charles states:

"This disturbing increase in male mortality from cancer of the lung had caused much speculation and inquiry. Since a comparable increase had been shown to have occurred in most of the countries from which reliable statistics were available it could be considered a world-wide phenomenon, at least of well-developed countries. The search continued for some widespread factor or factors, operating more on men than on women, whose effects had increased over the last quarter of a century. Suspicion continued to be thrown on tobacco, especially heavy cigarette smoking, as a result of statistical correlation between smoking and cancer of the lung revealed by investigations in this country and the U.S.A. These statistical inquiries were continuing and further statistical inquiries on a different and wider basis had been put in hand in this country and in America, although the results would not be available for some time."

* *Report of Ministry of Health (1st April, 1950, to 31st December, 1951)*: Part III, On the State of the Public Health (Annual Report of Chief Medical Officer for 1951). H.M.S.O., 6s. 6d. or post free 6s. 9d. Cmd. No. 8787.

Sir John Charles points out that there is still insufficient evidence of the cause. Excessive cigarette smoking may be one of the factors, but it cannot be the only factor, because cancer of the lung is known to occur in persons who have never smoked tobacco in any form.

THE WORLD HEALTH ORGANIZATION

THE Director-General in his Annual Report for 1952, with reference to tuberculosis, makes the following comments:

"W.H.O.'s field work in tuberculosis consisted principally of aid in establishing tuberculosis demonstration and training centres, and assistance, usually with U.N.I.C.E.F., in conducting B.C.G. vaccination campaigns, preferably in connection with general tuberculosis-control programmes. Help continued to be given to demonstration and training centres in Burma, Ecuador, El Salvador, India, Indonesia, Jamaica, Pakistan, Paraguay and Thailand. New centres were opened in Cairo, Egypt, and in Damascus, Syria. W.H.O. aid came to an end during the year at centres in India (Delhi) and in Turkey (Istanbul). Assistance in the form of personnel was provided for tuberculosis-control activities in Ceylon, Ecuador (teaching centre and B.C.G. production laboratory), Greece and Paraguay.

"B.C.G. vaccination campaigns were begun in Costa Rica, Indonesia, Iran, Iraq, Sarawak, Trinidad and Turkey; continued in Burma, El Salvador, India, Jamaica, Pakistan and the Philippines; and completed in Aden, China (Taiwan), Egypt and Hong Kong.

"During 1952, important studies on B.C.G. vaccination and tuberculin sensitivity were carried out by the Tuberculosis Research Office, Copenhagen. At the end of the year an important conference of tuberculosis workers from the Eastern Mediterranean, South-east Asia and Western Pacific Regions was held at Alexandria, Egypt."

NOTES AND NOTICES

INDUSTRIAL INJURIES INSURANCE

BOILER-SCALERS INSURED AGAINST PNEUMOCONIOSIS

BOILER-SCALING is added to the occupations which are covered for pneumoconiosis under the National Insurance (Industrial Injuries) Act by regulations made by the Minister of National Insurance, Mr. Osbert Peake.

As a result of these regulations, boiler-scalers who suspect that they have contracted pneumoconiosis—an occupational dust disease of the lungs—will be able to claim benefit under the Act.

NAPT CANADIAN EXCHANGE SCHOLARSHIPS

EACH year the National Association for the Prevention of Tuberculosis offers two Canadian Exchange Scholarshps—one for a British doctor to go to Canada for three months to study methods of tuberculosis control there, and another for a Canadian doctor to come to Great Britain for the same purpose. The value of each Scholarship is £350.

The Scholarships for 1953 have been awarded to Dr. Bertram Mann, Consultant Chest Physician at the Royal Halifax Infirmary, Yorkshire, who will be leaving England for three months in Canada early in September; and to Dr. J. J. Laurier, Assistant Medical Director of the Sacred Heart Hospital, Montreal.

Dr. Laurier arrived in England on May 1, and is visiting sanatoria, clinics and research centres in all parts of the United Kingdom. He is attending the Coronation as the representative of the Canadian Tuberculosis Association.

THE ROYAL SANITARY INSTITUTE
HEALTH CONGRESS TO MEET IN SCARBOROUGH

THE Council of the Royal Sanitary Institute have accepted an invitation from the Mayor of Scarborough to hold the Health Congress there in 1954, from April 27 to 30 inclusive.

The Congress will be attended by delegates from many parts of the world and is expected to attract about 2,500 visitors.

THE THORACIC SOCIETY

THE annual general meeting is being held in the William Dunn School of Pathology at Oxford on July 17 and 18. The programme includes a discussion on "Intracranial Complications of Thoracic Suppuration" to be opened by Mr. J. Pennybacker, followed by a discussion on "Intracranial Metastases from Lung Tumours," the opening speakers being Dr. J. Elkington, Mr. W. S. Lewin and Dr. P. M. Daniel.

There will also be short communications on: (1) "Chest Complications in Poliomyelitis," by Mr. T. Holmes Sellors; (2) "A Tumour of the Left Ventricle in a Boy aged Four," by Mr. B. J. Bickford; (3) "An Examination of X-ray Shadows in Pulmonary Tuberculosis," by Dr. R. N. Johnston; (4) "A.C.T.H. in Pulmonary Tuberculosis," by Dr. L. E. Houghton; as well as communications on "Chronic Bronchitis" to be opened by Dr. Neville Oswald, followed by Dr. Lynne Reid and Dr. J. R. May.